



07 JAN 1993

BAR CODE LABEL 		U.S. PATENT APPLICATION			
SERIAL NUMBER 07/714,486		FILING DATE 06/13/91		CLASS 514	GROUP ANY UNIT 125
APPLICANT	FRANS E. JANSSENS, BONHEIDEN, BELGIUM; GASTON S. M. DIELS, RAVELS, BELGIUM; JOSEPH E. LEENAERTS, RIJKEVORSEL, BELGIUM.				
	CONTINUING DATA*** VERIFIED				
	<div style="border: 1px solid black; padding: 5px; display: inline-block;">PRIORITY DOCUMENT</div> <div style="border: 1px solid black; padding: 5px; display: inline-block; transform: rotate(-5deg); margin-left: 20px;">REC'D 29 JUN 1992 WIPO PCT</div>				
FOREIGN/PCT APPLICATIONS*** VERIFIED					
STATE OR COUNTRY BEX	SHEETS DRAWING 0	TOTAL CLAIMS 9	INDEPENDENT CLAIMS 1	FILING FEE RECEIVED \$ 830.00	ATTORNEY DOCKET NO. JAB-758
ADDRESS	ROBERT L. MINIER ONE JOHNSON & JOHNSON PLAZA NEW BRUNSWICK, NJ 08933-7003				
TITLE	IMIDAZO(2,1-B) (3) BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE				
This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application as originally filed which is identified above.					
By authority of the COMMISSIONER OF PATENTS AND TRADEMARKS					
Date MAY - 5 1992		Certifying Officer 			

077714486

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET



07714486

A

JAB 758

501

5

IMIDAZO[2,1-b][3]BENZAZEPINE DERIVATIVES,
COMPOSITIONS AND METHOD OF USE

10 Background of the invention

In WO 88/03138 there are described benzo[5,6]cycloheptapyridines which possess antiallergic and anti-inflammatory activity. In EP-A-0,339,978 there are described (benzo- or pyrido)cyclohepta heterocyclics which are useful as PAF antagonists, antihistaminics and/or anti-inflammatory agents.

15

In the J. Med. Chem., 26 (1983), 974-980 there are described some 1-methyl-4-piperidinylidene-9-substituted pyrrolo[2,1-b][3]benzazepine derivatives having neuroleptic properties.

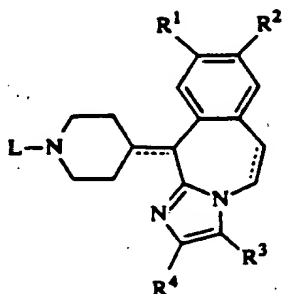
20

The compounds of the present invention differ structurally from the cited art-known compounds by the fact that the central 7-membered ring invariably contains a nitrogen atom of a fused imidazole ring, and by their favorable antiallergic activity.

Description of the invention

25

The present invention is concerned with novel imidazo[2,1-b][3]benzazepines of formula



(I).

the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein

each of the dotted lines independently represents an optional bond ;

R¹ represents hydrogen, halo or C₁-alkyl;

R² represents hydrogen, halo, C₁-alkyl or C₁-alkyloxy ;

R³ represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, formyl or hydroxycarbonyl ;

R⁴ represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, phenyl or halo ;

L represents hydrogen; C₁₋₆alkyl; C₁₋₆alkyl substituted with hydroxy, C₁₋₄alkyl-oxy, C₁₋₄alkyloxycarbonylamino, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylamino-carbonylamino, C₁₋₄alkylaminothiocabonylamino, aryl or aryloxy; C₃₋₆alkenyl; C₃₋₆alkenyl substituted with aryl ;

wherein each aryl is phenyl or phenyl substituted with halo, C₁₋₄alkyl or C₁₋₄alkyloxy ; or,

L represents a radical of formula

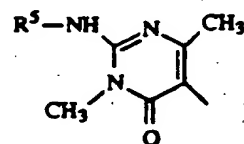


Alk represents C₁₋₄alkanediyl ;

Y represents O, S or NH ;

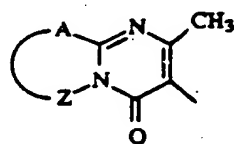
Het¹, Het² and Het³ each represent furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C₁₋₄alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C₁₋₄alkyl ; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C₁₋₄alkyl, C₁₋₄alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and

Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



(b-1)

or



(b-2)

wherein

R⁵ represents hydrogen or C₁₋₄alkyl ; and

A-Z represents S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH or CH₂-CH₂-CH₂-CH₂.

As used in the foregoing definitions halo defines fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C₁₋₆alkyl defines

C₁₋₄alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, for example, pentyl and hexyl; C₃₋₆alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 3,3-dimethyl-2-propenyl, hexenyl and the like; C₁₋₄alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 4 carbon atoms such as, for example, methylene, 1,1-ethanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like.

10 The term pharmaceutically acceptable addition salt as used hereinbefore defines the non-toxic, therapeutically active addition salt forms which the compounds of formula (I) may form. The compounds of formula (I) having basic properties may be converted into the corresponding therapeutically active, non-toxic acid addition salt forms by treating the free base form with a suitable amount of an appropriate acid following conventional
15 procedures. Examples of appropriate acids are for example, inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic,
20 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

The compounds of formula (I) having acidic properties may be converted in a similar manner into the corresponding therapeutically active, non-toxic base addition salt forms.
25 Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, N-methyl-D-glucamine, hydrabamine, amino acids, e.g. arginine, lysine. The term pharmaceutically acceptable addition salts also comprises the solvates which the compounds of formula (I) may form, e.g. the
30 hydrates, alcoholates and the like.

The term stereochemically isomeric forms as used hereinbefore defines the possible different isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of
35 compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the

compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

5 Some compounds of the present invention may exist in different tautomeric forms and all such tautomeric forms are intended to be included within the scope of the present invention.

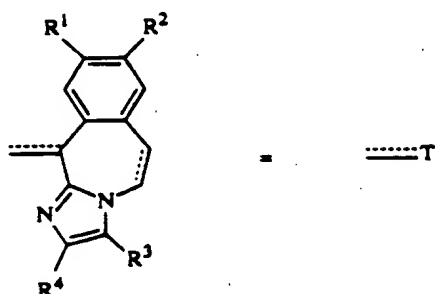
10 Interesting compounds of formula (I) are those compounds wherein L represents hydrogen; C₁₋₄alkyl; C₁₋₄alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylaminothiocarbonyl-amino or aryl; propenyl; propenyl substituted with aryl; wherein each aryl is phenyl or phenyl substituted with C₁₋₄alkyloxy; or,

15 L represents a radical of formula (a-1), (a-2) or (a-3); wherein Het¹, Het² and Het³ represent furanyl, thiazolyl or imidazolyl each optionally substituted with one or two C₁₋₄alkyl substituents; pyridinyl or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula
20 (b-1) or (b-2), wherein R⁵ represents hydrogen; and A-Z represents S-CH=CH, S-CH₂-CH₂ or CH=CH-CH=CH.

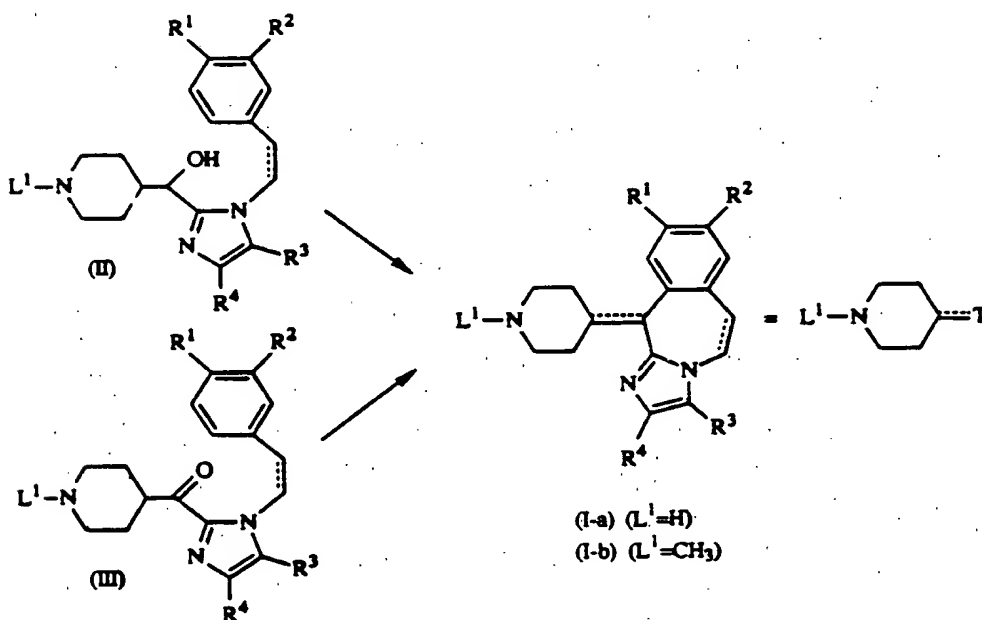
25 More interesting compounds are those interesting compounds wherein R² represents halo, C₁₋₄alkyl or C₁₋₄alkyloxy; and R⁴ represents hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl or halo.

Preferred compounds within the above identified groups are those compounds wherein L represents C₁₋₄alkyl.

30 In the following paragraphs there are described different ways of preparing the compounds of formula (I). In order to simplify the structural formulae of the compounds of formula (I) and the intermediates intervening in their preparation, the imidazo[2,1-b][3]benzazepine moiety will be represented by the symbol T hereinafter.



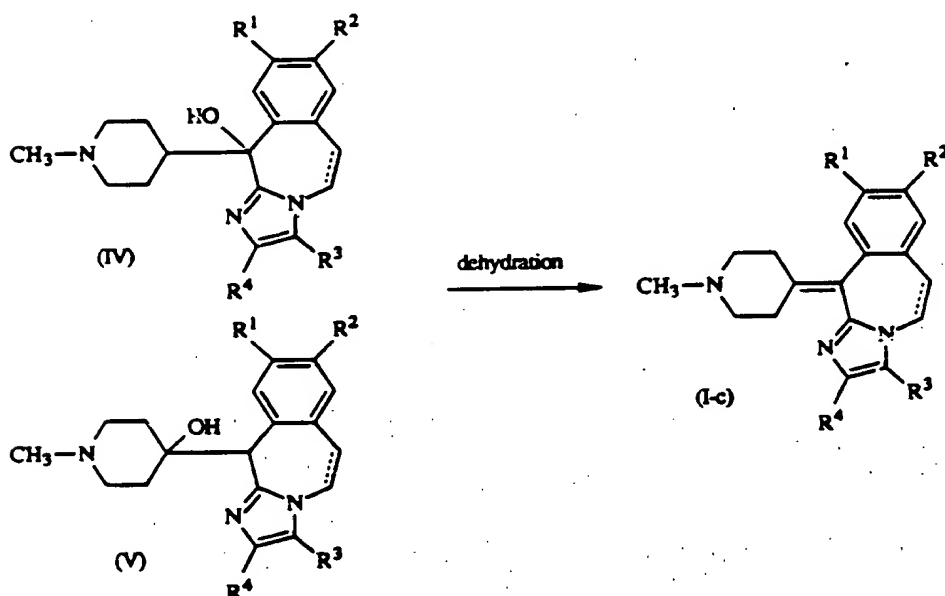
The compounds of formula (I) wherein L represents hydrogen or methyl, said compounds being represented by formulae (I-a) and (I-b) respectively and said L by L¹,
 5 can be prepared by cyclizing an alcohol of formula (II) or a ketone of formula (III).



Said cyclization reaction is conveniently conducted by treating the intermediate of
 10 formula (II) or (III) with an appropriate acid, thus yielding a reactive intermediate which
 cyclizes to a compound of formula (I-a) or (I-b). Appropriate acids are, for example,
 strong acids, in particular superacid systems, e.g. methanesulfonic acid, trifluoro-
 methanesulfonic acid, methanesulfonic acid / boron trifluoride, hydrofluoric acid / boron
 trifluoride, or Lewis acids, e.g. aluminum chloride and the like. In case of superacids the
 15 reaction is preferably conducted in an excess of said acid; in case of solid Lewis acids,
 e.g. aluminum chloride, the reaction can be conducted by fusing the starting material and
 the reagent, preferably in the presence of an additional salt such as sodium chloride.

In the foregoing and following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

- 5 Alternatively, the compounds of formula (I) wherein L represents methyl and wherein a double bond exists between the piperidiny1 and the imidazo[2,1-b][3]benzazepine moiety, said compounds being represented by formula (I-c), can be prepared by dehydrating an alcohol of formula (IV) or (V).

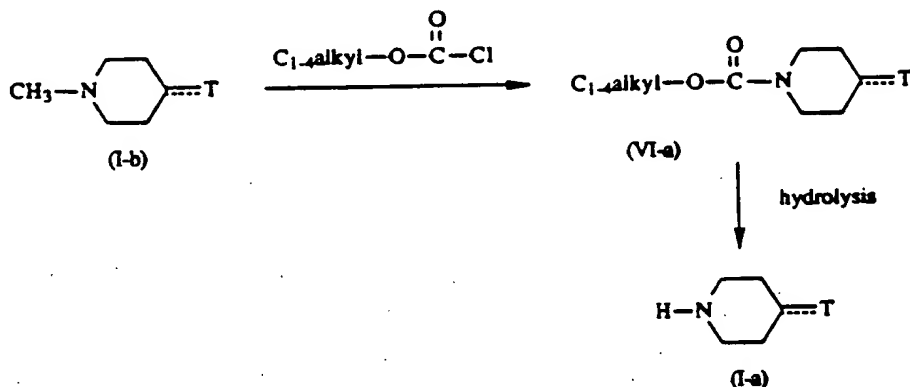


10

- Said dehydration reaction can conveniently be conducted employing conventional dehydrating reagents following art-known methodologies. Appropriate dehydrating reagents are, for example, acids, e.g. sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, carboxylic acids, e.g. acetic acid, trifluoroacetic acid and mixtures thereof; anhydrides, e.g. acetic anhydride, phosphorus pentoxide and the like; other suitable reagents, e.g. zinc chloride, thionyl chloride, boron trifluoride etherate, phosphoryl chloride pyridine, potassium bisulfate, potassium hydroxide. In some instances said dehydration reaction may require heating the reaction mixture, more particularly up to the reflux temperature.
- 15
- 20

The compounds of formula (I-c) can be converted into the compounds of formula (I-a) in a number of manners. A first method involves demethylating - carbonylating the

compounds of formula (I-b) with a C₁₋₄alkylchloroformate and subsequently hydrolyzing the thus obtained compound of formula (VI-a).



5

The reaction with the C₁₋₄alkylchloroformate is conveniently conducted by stirring and heating the starting material (I-b) with the reagent in an appropriate solvent and in the presence of a suitable base. Appropriate solvents are, for example, aromatic hydrocarbons, e.g. methylbenzene, dimethylbenzene, chlorobenzene; ethers, e.g.

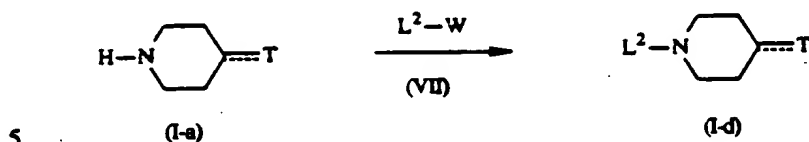
10 1,2-dimethoxyethane, and the like solvents. Suitable bases are, for example, alkali or earth alkaline metal carbonates, hydrogen carbonates, hydroxides, or organic bases such as, *N,N*-diethylethanamine, *N*-(1-methylethyl)-2-propanamine, and the like.

The compounds of formula (VI-a) are hydrolyzed in acidic or basic media following conventional methods. For example, concentrated acids such as hydrobromic or
15 hydrochloric acid or sulfuric acid can be used, or alternatively bases such as alkali metal or earth alkaline metal hydroxides in water, an alkanol or a mixture of water-alkanol may be used. Suitable alkanols are methanol, ethanol, 2-propanol and the like. In order to enhance the rate of the reaction it is advantageous to heat the reaction mixture in particular up to the reflux temperature.

20

The compounds of formula (I-b) may also be converted directly into the compounds of formula (I-a) by stirring and heating them with an α -halo-C₁₋₄alkyl chloroformate in an appropriate solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane; an aromatic hydrocarbon, e.g. methylbenzene, dimethylbenzene; an ether, e.g. 1,2-dimethoxyethane, optionally in the presence of a
25 base such as, for example, an alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide or an amine, e.g. *N,N*-diethylethanamine, *N*-(1-methylethyl)-2-propanamine, and the like.

The compounds of formula (I) wherein L is other than hydrogen, said compounds being represented by formula (I-d) and said L by L^2 , can be prepared by N-alkylating the compounds of formula (I-a) with a reagent of formula L^2-W (VII).

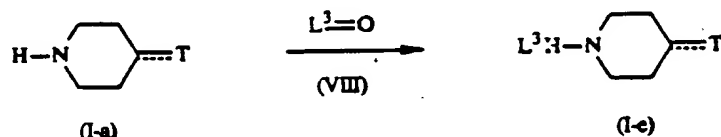


In formula (VII) and hereinafter W represents an appropriate leaving group such as, for example, halo, e.g. chloro, bromo and the like; or a sulfonyloxy group such as, for example, methanesulfonyloxy, 4-methylbenzenesulfonyloxy and the like.

10 Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitro-
15 benzene, 1-methyl-2-pyrrolidinone and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium
20 methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some
25 instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions.

30 The compounds of formula (I) wherein L is C_{1-6} alkyl or substituted C_{1-6} alkyl, said L being represented by the radical L^3H - and said compounds by formula (I-e), can also be prepared by reductive N-alkylation of the compounds of formula (I-a) with an appropriate ketone or aldehyde of formula $L^3=O$ (VIII). $L^3=O$ represents an intermediate of formula L^3H_2 wherein two geminal hydrogen atoms have been replaced by oxygen

(=O) and L^3 is a geminal bivalent C_{1-6} alkylidene radical which optionally may be substituted.

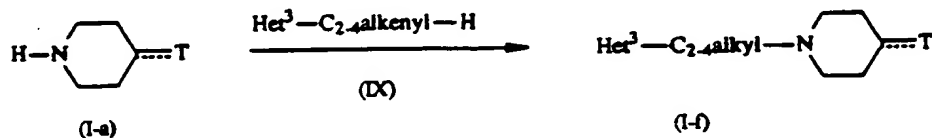


5

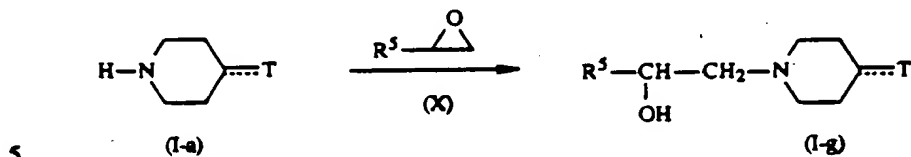
Said reductive N -alkylation reaction may conveniently be carried out by reducing a mixture of the reactants in a suitable reaction-inert solvent following art-known reductive N -alkylation procedures. In particular, the reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Suitable solvents are, for example, water, C_{1-6} alkanols, e.g. methanol, ethanol, 2-propanol and the like; esters, e.g. ethyl acetate, γ -butyrolactone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybis-ethane, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like; dipolar aprotic solvents, e.g. N,N -dimethylformamide, dimethyl sulfoxide and the like; carboxylic acids, e.g. acetic acid, propanoic acid and the like; or a mixture of such solvents. The term "art-known reductive N -alkylation procedures" means that the reaction is carried out either with sodium cyanoborohydride, sodium borohydride, formic acid or a salt thereof, e.g. ammonium formate and the like reducing agents, or alternatively under hydrogen atmosphere, optionally at an increased temperature and/or pressure, in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene, quinoline-sulphur and the like. In some instances it may also be advantageous to add an alkali metal salt to the reaction mixture such as, for example, potassium fluoride, potassium acetate and the like salts.

30

The compounds of formula (I) wherein L represents a radical $\text{Het}^3\text{-C}_{2-4}\text{alkyl}$, said compounds being represented by formula (I-f) can be prepared by the addition reaction of a compound of formula (I-a) to an appropriate alkene of formula (IX).

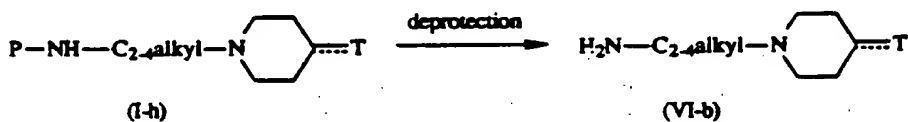


The compounds wherein L is 2-hydroxy-C₂₋₆alkyl, said compounds being represented by formula (I-g), can be prepared by reacting a compound of formula (I-a) with an epoxide (X) wherein R^S represents hydrogen or C₁₋₄alkyl.

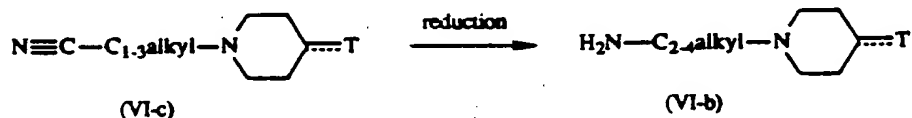


The reaction of (I-a) with respectively (IX) or (X) can be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for example, a ketone, e.g. 2-propanone, 4-methyl-2-pentanone; an ether, e.g. tetrahydrofuran; an alcohol, e.g. methanol, ethanol, 1-butanol; a dipolar aprotic solvent, e.g. *N,N*-dimethylformamide and the like.

The compounds of formula (I) wherein L is amino-C₂₋₄alkyl, said compounds being represented by formula (VI-b), can be prepared from a compound of formula (I-h) wherein L represents P-NH-C₂₋₄alkyl and P is a protective group such as, for example, C₁₋₄alkyloxycarbonyl, following art-known deprotection methods.

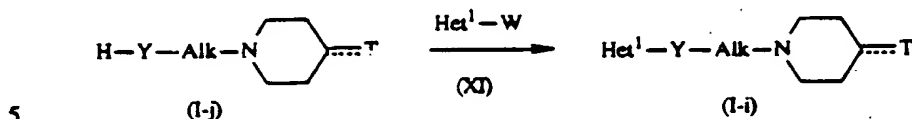


20 The compounds of formula (VI-b) can also be prepared by reducing a compound of formula (VI-c) wherein L represents cyanoC₁₋₃alkyl.

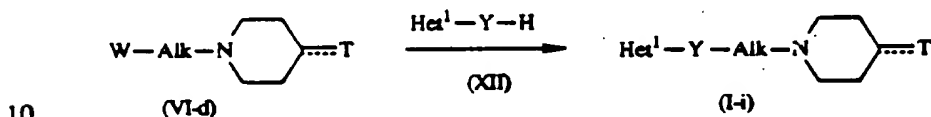


25 Said reduction can be conducted by stirring and, if desired, heating the starting material in a hydrogen containing medium in the presence of a catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel and the like, in a suitable solvent, e.g. methanol, ethanol and the like, or by reduction with a metal hydride, e.g. lithium aluminum hydride in an ether, e.g. tetrahydrofuran.

The compounds of formula (I) wherein L is a radical of formula $-\text{Alk}-\text{Y}-\text{Het}^1$, said compounds being represented by formula (I-i), can be prepared by alkylating a compound of formula (I-j) with a reagent of formula (XI).

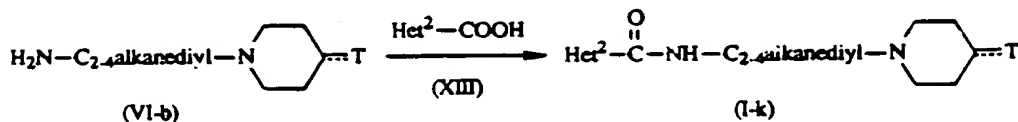


Alternatively, the compounds of formula (I-i) can also be prepared by reacting a compound of formula (VI-d) with a reagent of formula (XII).



The above alkylation reactions may conveniently be conducted in a reaction-inert solvent, e.g. methylbenzene, dimethylbenzene, 2-propanone, 4-methyl-2-pentanone, 1,4-dioxane, tetrahydrofuran, *N,N*-dimethylformamide, *N*-methyl-2-pyrrolidone, methanol, ethanol, 1-butanol and the like. The addition of an appropriate base, e.g. an alkali metal or earth alkaline metal carbonate or hydrogen carbonate, sodium hydride, *N,N*-diethylethanamine or *N*-(1-methylethyl)-2-propanamine may be used to pick up the acid liberated during the course of the reaction. In order to enhance the rate of the reaction the reaction mixture may be heated.

The compounds of formula (I) wherein L represents a radical of formula $-\text{Alk}-\text{NH}-\text{CO}-\text{Het}^2$, said compounds being represented by formula (I-k) can be prepared by *N*-acylating a compound of formula (VI-b) with a carboxylic acid of formula (XIII) or a reactive functional derivative thereof.



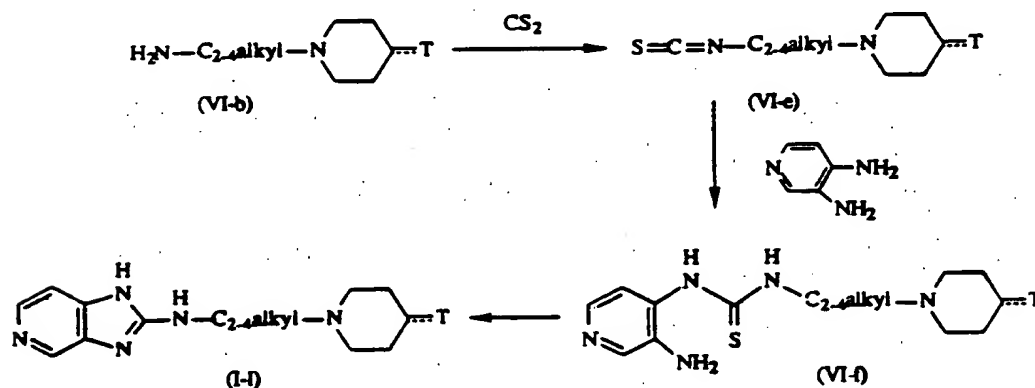
The reaction of (XIII) with (VI-b) may generally be conducted following art-known amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g. an anhydride or a carboxylic acid halide, which subsequently is reacted with (VI-b); or by reacting (XIII) and (VI-b) with a suitable reagent capable of

forming amides, e.g., *N,N*-methanetetraylbis(cyclohexamine), 2-chloro-1-methylpyridinium iodide and the like. Said reactions are conveniently conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like.

- 5 The addition of a base such as, for example, *N,N*-diethyl-ethanamine and the like may be appropriate.

The compounds of formula (I) wherein L represents C_{1-4} alkylamino(thio)carbonylamino can be prepared from the compounds of formula (VI-b) by reaction with a C_{1-4} alkyliso(thio)cyanate in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran.

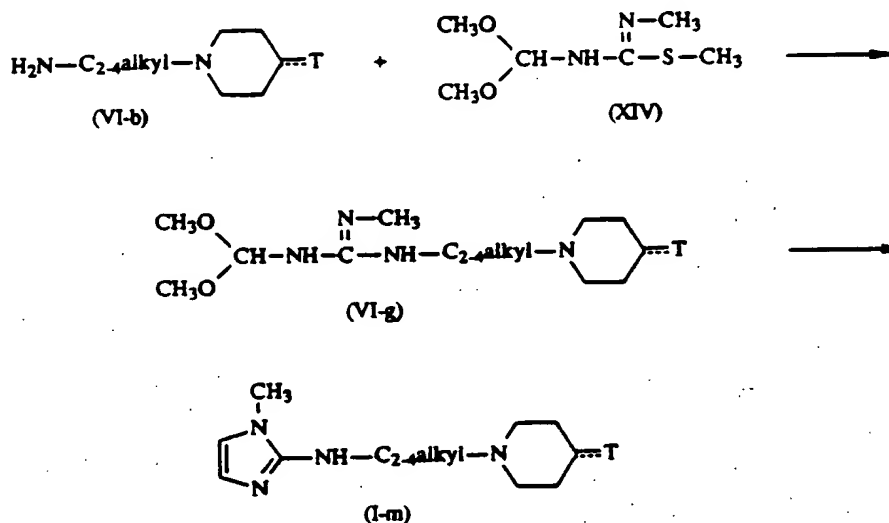
The compounds of formula (I) wherein Het¹ represents an imidazo[4,5-c]pyridin-2-yl radical and Y represents NH, said compounds being represented by formula (I-1) can be prepared from a compound of formula (VI-b) according to the following reaction scheme.



- 20 The isocyanate (VI-e) is prepared by reacting (VI-b) with carbon disulfide in the presence of a dehydrating reagent such as *N,N*-methanetetraylbis(cyclohexanamine) in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran. The isothiocyanate is reacted with 3,4-diaminopyridine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran, and the resulting thiourea is cyclized by treatment with an appropriate
- 25 metal oxide such as mercury(II)oxide.

The compound (VI-e) can also be employed to prepare compounds of formula (I) wherein L is C₁₋₄alkylaminothiocarbonylamino by reacting (VI-e) with a C₁₋₄alkylamine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran.

- 5 The compounds of formula (I) wherein Het¹ represents an imidazole and Y represents NH, said compounds being represented by formula (I-m) can be prepared from the compounds (VI-b) according to the following reaction scheme.



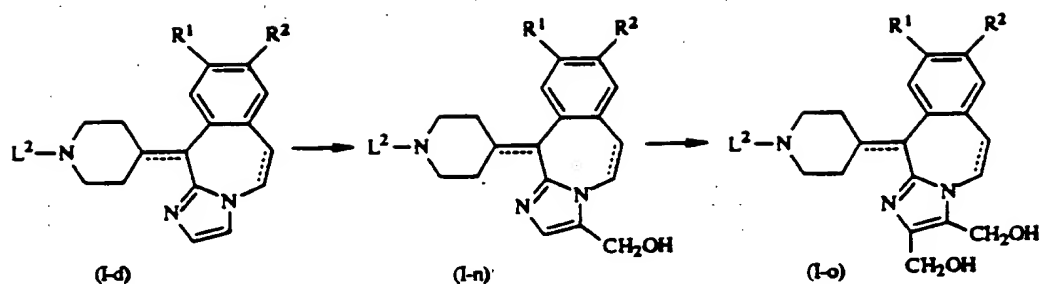
10

The compound (VI-b) is reacted with a reagent of formula (XIV) in a reaction-inert solvent such as an alcohol, e.g. 2-propanol and the thus obtained intermediate (VI-g) is cyclized by treatment with an acidic aqueous solution.

15

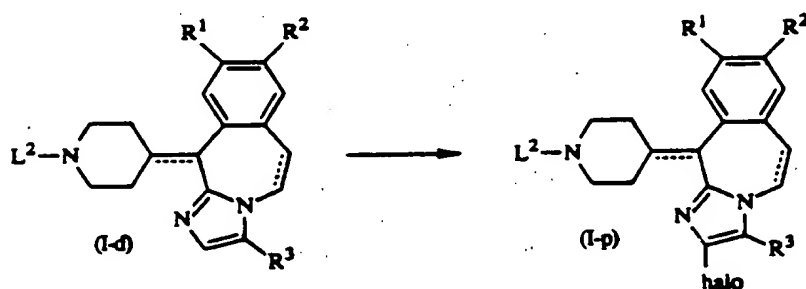
The compounds of formula (I) wherein R³ and/or R⁴ represent hydroxymethyl can be prepared by formylating the compounds of formula (I-d) with formaldehyde, optionally in the presence of an appropriate carboxylic acid - carboxylate mixture such as, for example, acetic acid - sodium acetate and the like. In order to enhance the rate of the reaction, the reaction mixture is advantageously heated up to the reflux temperature.

20



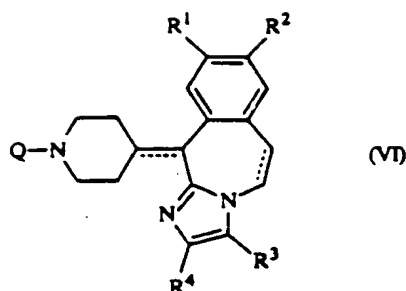
5 The thus obtained compounds (I-n) and (I-o) can be further oxidized to the corresponding aldehyde or carboxylic acid by reaction with suitable reagents such as, for example, manganese(IV)oxide, respectively, silver nitrate.

10 The compounds of formula (I) wherein R^4 is halo, said compounds being represented by formula (I-p), can be prepared by halogenating the compounds of formula (I-d).



15 Said halogenation reaction can conveniently be conducted by treating the starting material with dihalide in an appropriate solvent such as, for example, a carboxylic acid, e.g. acetic acid, optionally in admixture with a carboxylate salt, e.g. sodium acetate. In order to enhance the rate of the reaction, the reaction mixture may be heated.

20 The compounds of formula (VI-a to VI-g) intervening in the preparations described hereinbefore are novel and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein

5 R^1 , R^2 , R^3 and R^4 are as defined under formula (I); and

Q is (C₁₋₆alkyl or phenyl)oxycarbonyl or C₁₋₆alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)aminothiocarbonylamino or (CH₃O)₂CH-CH₂-NH-C(=NCH₃)-NH-.

10 Particularly interesting compounds of formula (VI) are those wherein Q represents C₁₋₄alkyloxycarbonyl, the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof.

15 In the following paragraphs there are described several methods of preparing the starting materials employed in the foregoing preparations.

The intermediates of formula (II) can be prepared from the corresponding ketones of formula (III) by reduction.



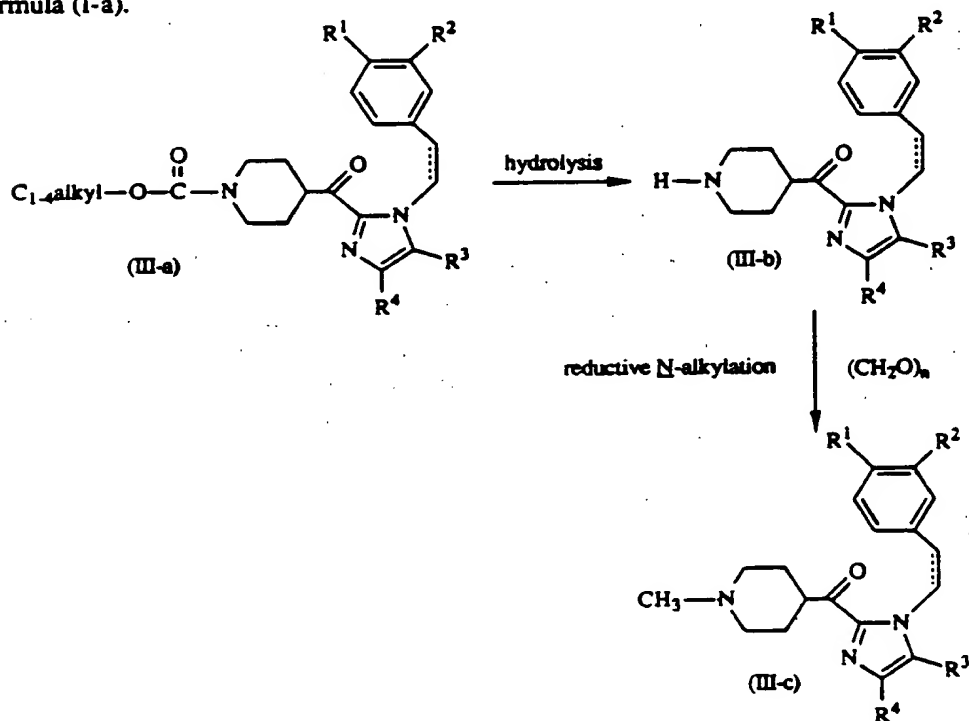
Said reduction can conveniently be conducted by reacting the starting ketone (III) with hydrogen in a solvent such as, for example, an alcohol, e.g. methanol, ethanol; an acid, e.g. acetic acid; an ester, e.g. ethyl acetate; in the presence of a hydrogenation catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel.

25 In order to enhance the rate of the reaction, the reaction mixture may be heated and, if desired, the pressure of the hydrogen gas may be raised.

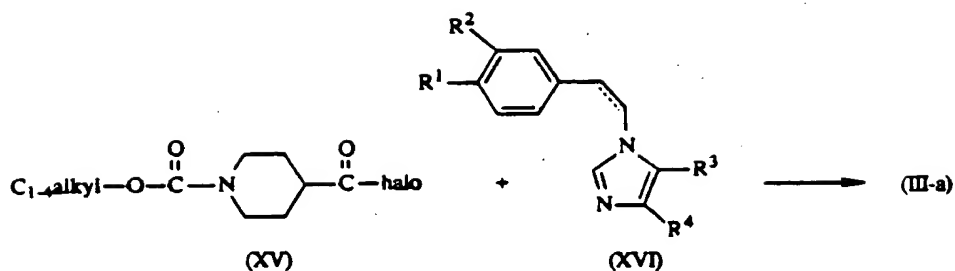
Alternatively, the alcohols of formula (II) can also be prepared by reducing the ketones (III) with a reducing agent such as, for example, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride and the like in a suitable solvent such as, for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; an alcohol, e.g. methanol, ethanol and the like.

The ketones of formula (III) wherein L^1 represents methyl, can be prepared from the ketones wherein L^1 represents hydrogen by reductive N-alkylation with formaldehyde following the methods described hereinbefore for the preparation of the compounds of formula (I-e).

The ketones of formula (III) wherein L^1 represents hydrogen are prepared by hydrolysis of a carbamate of formula (III-a) in acidic or basic media following conventional methods as described hereinbefore for the preparation of compounds of formula (I-a).



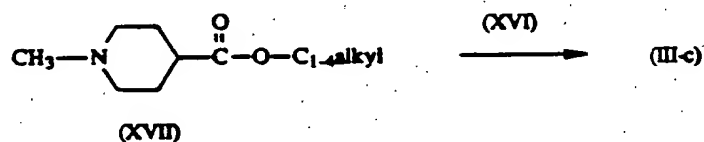
The intermediates of formula (III-a) can be prepared by reacting an acid halide of formula (XV) with an imidazole derivative of formula (XVI).



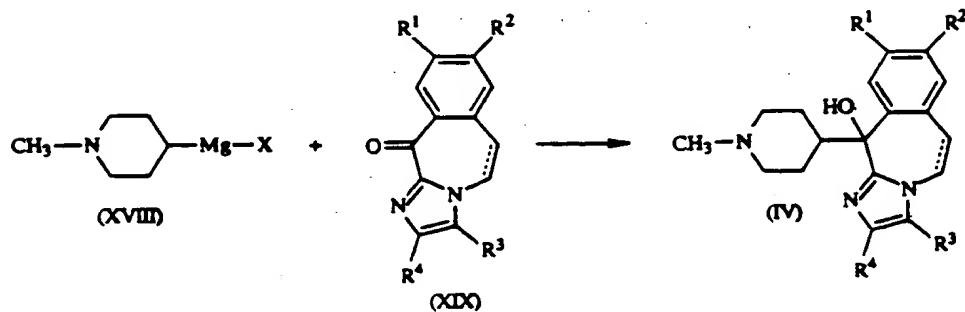
Said reaction is conveniently conducted by stirring and heating the reactants in the presence of a base such as, for example, an amine, e.g. *N,N*-diethylethanamine, *N*-methylmorpholine and the like, in a suitable solvent such as, for example, pyridine, acetonitrile or a mixture thereof.

The intermediates of formula (III-c) can be prepared from an ester of formula (XVII) by reaction with an imidazole of formula (XVI) in the presence of a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a suitable reaction-inert solvent, e.g. tetrahydrofuran, hexane, methylbenzene and the like, or a mixture thereof.

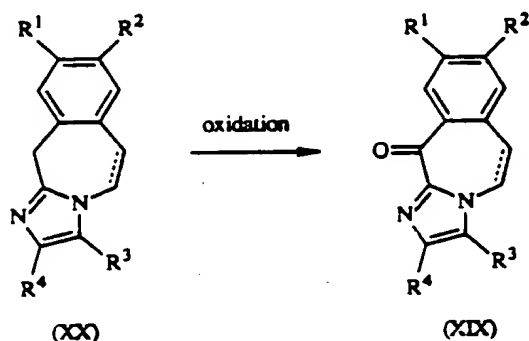
Said reaction is conveniently conducted at low temperatures. For example the reagent (XVI) may be added at a temperature between about -80°C to about -40°C to the strong base. Subsequently the ester is added and the reaction mixture is allowed to warm up gently to room temperature.



The intermediates of formula (IV) are prepared by addition of a Grignard reagent (XVIII) to a ketone of formula (XIX) in a reaction-inert solvent, e.g. tetrahydrofuran.

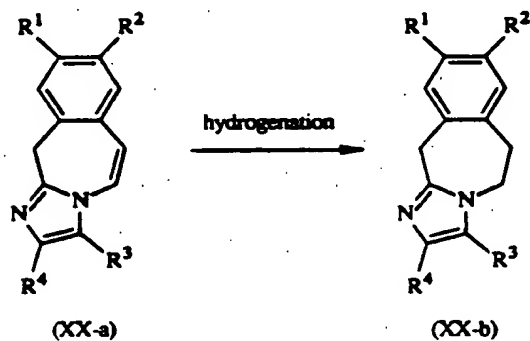


The tricyclic ketones of formula (XIX) in turn are prepared from intermediates of formula (XX) by oxidation with suitable oxidizing reagent in a reaction-inert solvent.

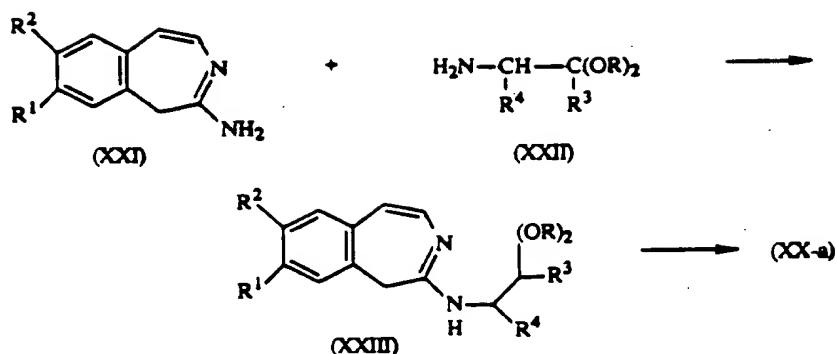


Suitable oxidizing reagents are, for example, manganese dioxide, selenium dioxide, ceric ammonium nitrate and the like. Reaction-inert solvents are, for example, halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like.

The compounds of formula (XX) wherein the dotted lines do not represent an optional bond, can be prepared from the corresponding compounds of formula (XX) wherein said dotted lines do represent an optional bond, following art-known hydrogenation procedures, e.g. by reaction with hydrogen in the presence of a hydrogenation catalyst.



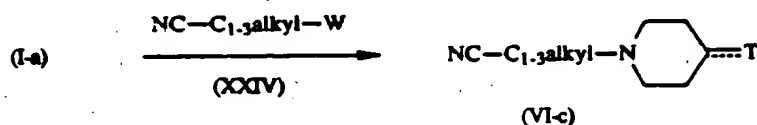
The intermediates of formula (XX-a) can be prepared from a benzazepine of formula (XXI) by reaction with a reagent of formula (XXII) and cyclization of the thus obtained intermediate (XXIII) in an acidic medium. In (XXII) R represents C₁₋₄alkyl or both radicals R taken together represent C₂₋₆alkanediyl, e.g. 1,2-ethanediyl, 1,3-propanediyl, 2,2-dimethyl-1,3-propanediyl.



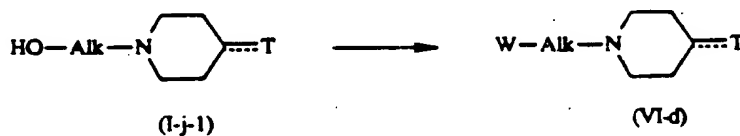
The preparation of (XXIII) is conveniently conducted by stirring and heating the reactants in a reaction-inert solvent such as, for example, an alcohol, e.g. methanol, ethanol and the like.

The cyclization reaction to the intermediates of formula (XX) is conducted by stirring and heating the starting material (XXIII) in a carboxylic acid such as, for example, acetic acid, propanoic acid, optionally in admixture with a mineral acid such as, for example, hydrochloric acid.

The intermediates of formula (VI-c) can be prepared by N-alkylating a compound of formula (I-a) with a reagent of formula (XXIV) following the procedures described hereinbefore for the preparation of the compounds of formula (I-d).



The intermediates of formula (VI-d) can be prepared from the compounds of formula (I-j) wherein Y is oxygen by reaction with a halogenating reagent such as, for example, thionyl chloride, phosphorous trichloride, phosphoryl chloride and the like, or by reaction with a sulfonating reagent such as, for example, methanesulfonyl chloride, 4-methyl-benzenesulfonyl chloride and the like.



The compounds of formula (I) and (VI-a), the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. In particular they are active antiallergic agents, which activity can clearly be demonstrated by the test results obtained in a number of indicative tests.

5

Antihistaminic activity can be demonstrated in 'Protection of Rats from Compound 48/80 - induced Lethality' test (Arch. Int. Pharmacodyn. Ther., 234, 164-176, 1978);

10 'Histamine - induced Lethality in Guinea Pigs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981);

and the broad antiallergic activity can be demonstrated in 'Passive cutaneous anaphylaxis in Rats' test (Drug Dev. Res., 5, 137-145, 1985) (For some compounds this test has been modified by replacing compound 48/80 by Ascaris allergens) and the

15 'Ascaris Allergy in Dogs' test (Arch. Int. Pharmacodyn. Ther., 251, 39-51, 1981 and Drug Dev. Res., 8, 95-102, 1986).

20 The compounds of the present invention show a broad spectrum antiallergic profile as is evidenced by the results obtained in the diversity of test procedures cited hereinbefore.

A second advantageous feature of the compounds of the present invention resides in their excellent oral activity; the present compounds when administered orally have been found to be practically equipotent with the same being administered subcutaneously.

25 A particularly important asset of the present compounds is their lack of sedating properties, a troublesome side effect associated with many antihistaminic and antiallergic compounds. The non-sedating properties of the present compounds can be demonstrated, for example, by the results obtained in studying the sleep - wakefulness cycle of the rat (Psychopharmacology, 97, 436-442, (1989)).

30

Another interesting feature of the present compounds relates to their fast onset of action and the favorable duration of their action.

35 In view of their antiallergic properties, the compounds of formula (I) and (VI-a) and their acid addition salts are very useful in the treatment of broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antiallergic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable

solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

5 The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I) and (VI-a) or a pharmaceutically acceptable acid addition salt form thereof.

Those of skill in treating allergic diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is
10 contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by
15 weight.

Experimental part

A. Preparation of the intermediates

20 Example 1

a) To a cooled mixture of 54.2 grams of 1-(2-phenylethyl)-1H-imidazole, 34.7 grams of N,N-diethylethanamine and 50 ml of pyridine there were added dropwise 69.2 grams of ethyl 4-chlorocarbonyl-1-piperidinecarboxylate (temp. $\leq 20^{\circ}\text{C}$) and then 30 ml of acetonitrile. The whole was stirred for 2 hours at room temperature and for 4 hours at
25 reflux temperature. After cooling, there were added 30 ml NaOH 50% and refluxing was continued for 1/2 hour. The cooled reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 97:3). The eluent of the desired fraction was evaporated
30 and the residue was dried, yielding 38 grams (33.9 %) of ethyl 4-[[1-(2-phenylethyl)-1H-imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 1).

b) A mixture of 9 grams of intermediate (1) and 50 ml of hydrobromic acid 48% was stirred for 5 hours at 80°C . The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and dried, yielding
35 10.85 grams (97.5%) of [1-(2-phenylethyl)-1H-imidazol-2-yl] (4-piperidinyl)-methanone dihydrobromide; mp. 275.3°C (interm. 2).

c) A mixture of 55 grams of intermediate (2), 70 ml of formaldehyde and 70 ml of formic acid was stirred for 5 hours at reflux temperature. After cooling, the reaction mixture was diluted with water and basified with NaOH(aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 90:10). The eluent of the desired fraction was evaporated and the residue was dried, yielding 30 grams (82.0%) of (1-methyl-4-piperidinyl) [1-(2-phenylethyl)-1H-imidazol-2-yl]methanone (interm. 3).

In a similar manner there was also prepared :
10 [1-[2-(4-fluorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 4).

Example 2

A mixture of 70.6 grams of intermediate (2) and 700 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 grams of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 54 grams (75.7 %) of α -[1-(2-phenylethyl)-1H-imidazol-2-yl]-4-piperidinemethanol; mp. 144.6 °C (interm. 5).

Example 3

A mixture of 28.9 grams of 2-(4-methylphenyl)ethanol methanesulfonate, 18.6 grams of 1H-imidazole, 22.7 grams of potassium carbonate and 600 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was evaporated and the residue was taken up in water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was distilled (13.3 Pa; 120 °C), yielding 20.1 grams (83.0%) of 1-[2-(4-methylphenyl)ethyl]-1H-imidazole (interm. 6).

In a similar manner there were also prepared :

30 1-[2-(3-methylphenyl)ethyl]-1H-imidazole; bp. 120°C at 13.3 Pa (interm. 7).
1-[2-(4-bromophenyl)ethyl]-1H-imidazole (interm. 8).
1-[2-(3-chlorophenyl)ethyl]-1H-imidazole; bp. 134°C at 13.3 Pa (interm. 9).

Example 4

35 A mixture of 67 grams of 1-(2-chloroethyl)-3-methoxybenzene, 53.1 grams of 1H-imidazole, 99 grams of sodium carbonate, 500 ml of 4-methyl-2-pentanone and a few crystals of potassium iodide was stirred for 48 hours at reflux temperature. After

cooling, the reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was distilled (13.3 Pa; 160 °C), yielding 49.5 grams (62.8%) of 1-[2-(3-methoxyphenyl)ethyl]-1H-imidazole (interm. 10).

5

Example 5

a) To a stirred amount of 250 ml of N,N-dimethylformamide under nitrogen, there were added portionwise 6 grams of a dispersion of sodium hydride in mineral oil and 82.1 grams of 4-methylimidazole and then dropwise 132 grams of phenyloxirane. The whole
10 was stirred for 50 hours and then diluted with 1000 ml of water. The precipitate was filtered off, washed with water and 2,2'-oxybispropane and recrystallized from a mixture of acetonitrile and ethanol. The product was filtered off and dried, yielding 58.1 parts (28.7 %) of 5-methyl- α -phenyl-1H-imidazole-1-ethanol; mp. 192.7 °C (interm. 11).

15 b) A mixture of 57.1 grams of intermediate (11), 130 ml of 2-propanol saturated with HCl and 500 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 5 grams of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was diluted with water and the whole was basified with
20 NaOH(aq.). The product was extracted with dichloromethane and the extracted was dried, filtered and evaporated. The residue was co-evaporated with methylbenzene (3x), yielding 52.9 grams (100%) of 5-methyl-1-(2-phenylethyl)-1H-imidazole (interm. 12).

Example 6

25 To a cooled mixture (ice-bath) of 10.1 grams of intermediate (10), 12 grams of N,N-diethylethanamine and 150 ml of acetonitrile there were added dropwise 21.95 grams of ethyl 4-chloro-carbonyl-1-piperidinecarboxylate, keeping the temperature below 20 °C). After stirring for 2 hours at room temperature and 4 hours at reflux temperature, there were added dropwise 10 ml NaOH. The whole was refluxed for 1/2
30 hour, cooled and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 22 grams (100%) of ethyl 4-[[1-[2-(3-methoxyphenyl)ethyl]-1H-imidazol-2-yl]-carbonyl]-1-piperidinecarboxylate (interm. 13).

In a similar manner there were also prepared :

35 ethyl 4-[[1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidine-carboxylate (interm. 14),

1-acetyl-4-[[1-[2-(4-methylphenyl)ethyl]-1H-imidazol-2-yl]carbonyl]piperidine (interm. 15),

ethyl 4-[[5-methyl-1-(2-phenylethyl)-1H-imidazol-2-yl]carbonyl]-1-piperidine-carboxylate (interm. 16),

5 ethyl 4-[[1-[2-(3-methylphenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidine-carboxylate (interm. 17), and

ethyl 4-[[1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl]carbonyl]-1-piperidine-carboxylate (interm. 18).

10 Example 7

A mixture of 4.4 grams of intermediate (13) and 120 ml of hydrochloric acid 12N was stirred for 72 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water, basified with NaOH and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column
15 chromatography (silica gel; CH₂Cl₂ / CH₃OH(NH₃) 90:10). The eluent of the desired fraction was evaporated, yielding 2.63 grams (83.9 %) of [1-[2-(3-methoxyphenyl)-ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone (interm. 19).

In a similar manner there were also prepared :

[1-[2-(4-methylphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone

20 dihydrochloride (interm. 20), and

[1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone (interm. 21).

Example 8

A mixture of 130 grams of intermediate (16) and 1000 ml of hydrobromic acid 48% was
25 stirred for 24 hours at 80 °C. The reaction mixture was evaporated and the residue was recrystallized from 2-propanol. After cooling, the precipitate was filtered off and dried, yielding 124.2 grams (95.6%) of [5-methyl-1-(2-phenylethyl)-1H-imidazol-2-yl] (4-piperidinyl)-methanone dihydrobromide (interm. 22).

In a similar manner there were also prepared :

30 [1-[2-(3-methylphenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide (interm. 23), and

[1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl] (4-piperidinyl)methanone dihydrobromide hemihydrate (interm. 24).

35 Example 9

A mixture of 5.24 grams of intermediate (24), 2 grams of polyoxymethylene, 3 grams of potassium acetate, 2 ml of a solution of thiophene in methanol 4% and 150 ml of

- methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 grams of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and the whole was basified with K_2CO_3 . The product was
- 5 extracted with dichloromethane and the extract was dried, filtered and evaporated, yielding 3.2 grams (85.0%) of [1-[2-(4-bromophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidiny)-methanone (interm. 25).
- In a similar manner there were also prepared :
- [1-[2-(3-chlorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidiny)methanone
- 10 (interm. 26), and
- [1-[2-(3-methoxyphenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidiny)methanone (interm. 27).

Example 10

- 15 a) A mixture of 3.16 grams of 1H-3-benzazepin-2-amine, 4.17 grams of 2,2-dimethoxyethanamine and 50 ml of methanol was stirred for 16 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired
- 20 fraction was evaporated and the residue was stirred in hexane. The precipitate was filtered off, yielding 4.9 grams (100%) of N-(2,2-dimethoxyethyl)-1H-3-benzazepin-2-amine (interm. 28).
- b) A mixture of 4.9 grams of intermediate (28), 70 ml of acetic acid and 9 ml of hydrochloric acid 36% was stirred for 18 hours at 70°C. The reaction mixture was
- 25 evaporated and the residue was taken up in water. The whole was basified with NaOH(aq.) and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was
- 30 treated with active charcoal in 1,1'-oxybisethane. The whole was filtered and the filtrate was evaporated. The residue was triturated in hexane. The product was filtered off and dried, yielding 1.04 grams (28.5 %) of 11H-imidazo[2,1-b][3]benzazepine; mp. 85.5 °C (interm. 29).
- c) A mixture of 5 grams of intermediate (29), 20 grams of manganese dioxide and 150 ml of trichloromethane was stirred for 50 hours at reflux temperature. The whole was
- 35 filtered over diatomaceous earth, 20 grams of manganese dioxide were added and refluxing was continued for 48 hours (2x). The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the

residue was triturated in 1,1'-oxybisethane and then boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.61 grams (53.2%) of 11H-imidazo[2,1-b][3]benzazepin-11-one; mp. 218.9 °C (interm. 30).

- d) A mixture of 10 ml of tetrahydrofuran and 1.24 grams of magnesium was stirred under a nitrogen atmosphere. 1 crystal of iodine and then dropwise 1.2 grams of bromoethane were added and at reflux temperature there was added a solution of 6.7 grams of 4-chloro-1-methylpiperidine in 25 ml of tetrahydrofuran. After refluxing for 1 hour, the reaction mixture was cooled (0 °C). Then there were added 25 ml of tetrahydrofuran and portionwise 9.8 parts of intermediate (30), keeping the temperature below 10 °C. The whole was stirred for 1 hour at room temperature and decomposed with NH₄Cl (aq.). The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH (NH₃) 95:5). The eluent of the second fraction was evaporated and the residue was crystallized from acetonitrile in 2 fractions, yielding 4.76 parts (32.2%) of 11-(1-methyl-4-piperidiny)-11H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 155.2 °C (interm. 31).

Example 11

- Following the procedure of example 10 (c) and (d) 2-phenyl-11H-imidazo[2,1-b][3]benzazepine-11-one was converted into 11-(1-methyl-4-piperidiny)-2-phenyl-11H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 239.8 °C (interm. 32).

- A mixture of 6 grams of intermediate (32) and 300 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 3 grams of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH(NH₃) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 3.2 grams (53.5%) of 6,11-dihydro-11-(1-methyl-4-piperidiny)-2-phenyl-5H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 225.3 °C (interm. 33).

Example 12

- a) To a cooled (0°C) mixture of 46.2 grams of 3-fluorobenzenethanol, 40 ml of N,N-diethylethanamine and 500 ml of dichloromethane, there were added dropwise 41.2 grams of methanesulfonyl chloride, keeping the temperature below 5°C. After stirring for

18 hours at room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 81 grams (100%) of 2-(3-fluorophenyl)ethanol methanesulfonate (ester) (interm. 34).

- 5 b) A mixture of 72 grams of intermediate (34), 45 grams of 1H-imidazole, 55.5 grams of potassium carbonate and 1000 ml of tetrahydrofuran was stirred overweekend at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5). The eluent of
10 the desired fraction was evaporated and the residue was distilled (53.2 Pa; 130 °C), yielding 37.8 parts (60.2%) of 1-[2-(3-fluorophenyl)ethyl]-1H-imidazole (interm. 35).
c) To a cooled (-70 °C) mixture of 5.5 grams of 2-methyl-N-(1-methylethyl)ethanamine and 100 ml of tetrahydrofuran under a nitrogen atmosphere there were added dropwise
15 22 ml of butyllithium and after stirring for 15 min. at -40 °C, 9.5 grams of intermediate (35) at -70°C. Stirring at -70 °C was continued for 1 hour and then there were added 9.4 grams of ethyl 1-methyl-4-piperidinecarboxylate. The whole was stirred for 18 hours at room temperature, decomposed with water and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried,
20 filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH 80:20). The eluent of the desired fraction was evaporated, yielding 8 grams (50.7%) of [1-[2-(3-fluorophenyl)ethyl]-1H-imidazol-2-yl](1-methyl-4-piperidinyl)methanone (interm. 36).

B. Preparation of the final compounds

25 Example 13

- A mixture of 2.5 grams of intermediate (26) and 10 ml of trifluoromethanesulfonic acid was stirred for 72 hours at 110°C under nitrogen. After cooling, the reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was
30 extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH (NH₃) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.95 gram (40.4%) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine; mp. 186.6°C (comp. 3.10).

35

Example 14

A mixture of 2 grams of intermediate (27) and 10 ml of methanesulfonic acid was stirred for 1 hour at 100°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the
5 extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH(NH₃) 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 1 gram (30.8%) of
10 6,11-dihydro-8-methoxy-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 190.3°C (comp. 3.01).

Example 15

A mixture of 8 grams of intermediate (36), 24 grams of aluminum chloride and 10.3 grams of sodium chloride was stirred at 140°C until the whole was melted. Stirring was
15 continued for 1 hour at 120°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH(NH₃) 90:10). The eluent of the desired fraction was evaporated and the residue was triturated
20 in 2,2'-oxybispropane and recrystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 0.58 gram (10.8%) of 8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine; mp. 152.4°C (comp. 3.15).

Example 16

A mixture of 3.5 grams of intermediate (5) and 10 ml of trifluoromethanesulfonic acid was stirred for 18 hours at 110°C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was washed with water, dried, filtered and evaporated. The
30 residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was recrystallized from ethanol, yielding 0.8 gram (13.3%) of 6,11-dihydro-11-(4-piperidinyl)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 220.2°C (comp. 5.01).

Example 17

A mixture of 2.2 grams of intermediate (33), 10 ml of sulfuric acid and 10 ml of methanesulfonic acid was stirred for 2 hours at 70°C. The reaction mixture was poured

into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH(NH₃) 90:10). The eluent of the desired fraction was evaporated and the residue
5 was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.73 gram (34.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-2-phenyl-5H-imidazo[2,1-b][3]benzazepine; mp. 171.5°C (comp. 4.01).

Example 18

10 A mixture of 14.7 grams of intermediate (31) and 150 ml of acetic anhydride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ /
15 CH₃OH(NH₃) 95:5). The eluent of the first fraction was evaporated and the residue was taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was treated with activated charcoal. After filtration, the solution was evaporated and the residue was triturated in 2,2'-oxybispropane. The product was filtered off and dried, yielding 1.6 grams (11.5%) of product. The second fraction was also evaporated and the residue
20 taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was combined with the 2,2'-oxybispropane-filtrate of the first fraction, and evaporated, yielding an additional 8.2 grams (59.1%) of product. Total yield : 9.8 grams (70.6%) of 11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine; mp. 135.8°C (comp. 6.01).

25

Example 19

To a stirred and refluxing mixture of 7.2 grams of compound (3.10), 4.6 grams of N,N-diethylethanamine and 200 ml of methylbenzene there were added dropwise 12.5 grams of ethyl chloroformate. After refluxing for 1 hour and subsequent cooling, the reaction
30 mixture was diluted with water. The whole was basified with K₂CO₃ and then extracted with methylbenzene. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 6.62 grams (77.4%) of ethyl 4-(8-chloro-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-
35 carboxylate; mp. 140.3°C (comp. 3.11).

Example 20

- 5 a) A mixture of 2.5 grams of compound (1.03) and 50 ml of formaldehyde 40% was stirred for 1 week at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NH_4OH , stirred for 1/2 hour and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.45 grams (16.3%) of ethyl 4-[5,6-dihydro-3-(hydroxymethyl)-11H-imidazo[2,1-b][3]benzazepin-11-ylidene]-1-piperidinecarboxylate; mp. 191.9°C (comp. 4.11).
- 10 b) A mixture of 20 grams of compound (1.03) and 400 ml of formaldehyde 40% was stirred for 2 weeks at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NH_4OH , the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}$ 95:5 \rightarrow $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}(\text{NH}_3)$ 95:5). The eluent of the third fraction was evaporated, yielding 4.1 grams (17.2%) of ethyl 4-[5,6-dihydro-2,3-bis(hydroxymethyl)-11H-imidazo-
- 15 [2,1-b][3]benzazepin-11-ylidene]-1-piperidinecarboxylate (comp. 4.18).
- 20

Example 21

- A mixture of 13 grams of compound (1.03), 13 grams of potassium hydroxide and 100 ml of 2-propanol was stirred for 6 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with
- 25 dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}(\text{NH}_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was filtered off and dried, yielding 3.52 grams (18.3%) of 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]-
- 30 benzazepine (E)-2-butenedioate (1:2) dihydrate; mp. 192.5°C (comp. 1.04).

Example 22

- A mixture of 60 grams of compound (6.02) and 500 ml of hydrobromic acid 48% was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the
- 35 residue was taken up in water. After basifying with NaOH (aq.), the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}(\text{NH}_3)$

95:5 \rightarrow CH_2Cl_2 / $\text{CH}_3\text{OH}(\text{NH}_3)$ 90:10). The eluent of the first fraction was evaporated and the residue was converted into the dihydrobromide salt in ethanol. The salt was filtered off and dried, yielding 27.3 grams (37.7%) of 11-(4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine dihydrobromide hemihydrate; mp. 246.9°C (comp. 6.03).

5

Example 23

A mixture of 6.1 grams of compound (3.11) and 100 ml of hydrochloric acid 12N was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.9 grams (59.0%) of 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine; mp. 197.1°C (comp. 3.12).

15

Example 24

To a stirred and cooled (ice-bath) mixture of 5.6 grams of compound (2.12), 50 ml of dichloromethane and 2.5 grams of N,N-diethylethanamine there was added dropwise a solution of 2.38 grams of ethyl chloroformate in 20 ml of dichloromethane. Stirring was continued for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 2.85 grams (40.5%) of ethyl 4-(5,6-dihydro-9-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinecarboxylate; mp. 156.5°C (comp. 2.13).

20
25

Example 25

A mixture of 1.79 grams of 3-(2-chloroethyl)-2-oxazolidinone, 2.65 grams of compound (1.04), 1.3 grams of sodium carbonate, 150 ml of 4-methyl-2-pentanone and 1 gram of potassium iodide was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2 / $\text{CH}_3\text{OH}(\text{NH}_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (2:3) salt in ethanol. The salt was filtered off and dried, yielding 3.4 grams (61.5%) of 3-[2-[4-[5,6-dihydro-11H-imidazo[2,1-b]

30
35

[3]benzazepin-11-ylidene]-1-piperidinyl]ethyl]-2-oxazolidinone (E)-2-butenedioate (2:3); mp. 188.8°C (comp. 1.20).

Example 26

- 5 A mixture of 2.3 grams of 6-(2-chloroethyl)-7-methylthiazolo[3,2-a]pyrimidin-5-one, 2.65 grams of compound (1.04), 1.3 grams of sodium carbonate and 100 ml of 4-methyl-2-pentanone was stirred for 24 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified
10 by column chromatography (silica gel; CH₂Cl₂ / CH₃OH(NH₃) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 1.89 grams (41.3%) of 6-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 181.8°C (comp. 1.13).

Example 27

- A mixture of 0.83 gram of chloroacetonitrile, 2.65 grams of compound (1.04), 1.1 grams of N,N-diethylethanamine and 80 ml of N,N-dimethylacetamide was stirred for 18 hours at room temperature. The reaction mixture was poured into water and the
20 product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.0 grams (65.7%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineacetonitrile; mp. 220.4°C (comp. 1.26).

Example 28

- A mixture of 1.0 gram of 3-chloro-2-methyl-1-propene, 2.6 grams of compound (1.04), 1.6 grams of sodium carbonate and 50 ml of N,N-dimethylacetamide was stirred for 20 hours at 50°C. After cooling, there were added 100 ml of ethyl acetate. The whole was washed with water (3x), dried, filtered and evaporated. The residue was purified by
30 column chromatography (silica ge.; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butene-dicate (2:3) salt in 2-propanol. The salt was filtered off and dried, yielding 2.8 grams (56.7%) of 6,11-dihydro-11-[1-(2-methyl-2-propenyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (2:3); mp. 179.5°C (comp. 1.08).

Example 29

A mixture of 1.57 grams of 4-chloro-2-methyl-2-butene (dissolved in *N,N*-dimethylformamide), 2.65 grams of compound (1.04), 1.1 grams of sodium carbonate, 0.01 gram of potassium iodide and 100 ml of *N,N*-dimethylacetamide was stirred for 18
5 hours at room temperature. The reaction mixture was poured into water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel ; CH_2Cl_2 / CH_3OH / $\text{CH}_3\text{OH}(\text{NH}_3)$ 90:10:1; HPLC ; Lichroprep RP18 ; $\text{CH}_3\text{COONH}_4$ in H_2O 0.5% / CH_3OH / CH_3CN 40:55:5). The eluent of the desired fraction was evaporated and the
10 residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.25 gram (7.5%) of 6,11-dihydro-11-[1-(3-methyl-2-butenyl)-4-piperidinyldene]-5H-imidazo[2,1-b][3]benzazepine; mp. 127.2°C (comp. 1.09).

Example 30

15 A mixture of 19 grams of compound (2.03), 6 grams of chloroacetonitrile, 8 grams of *N,N*-diethylethanamine and 100 ml of *N,N*-dimethylformamide was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ;
20 CH_2Cl_2 / CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 4.15 grams (19.2%) of 4-(9-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]-benzazepin-11-ylidene)-1-piperidineacetonitrile; mp. 198.3°C (comp. 2.08).

25 Example 31

To a stirred mixture of 2.83 grams of compound (2.03), 2.12 grams of sodium carbonate, 50 ml of *N,N*-dimethylformamide and 1 gram of potassium iodide there were added dropwise 25.4 grams of 4-chloro-2-methyl-2-butene (dissolved in *N,N*-dimethylformamide). Stirring at room temperature was continued for 50 hours. The reaction
30 mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH_2Cl_2 / $\text{CH}_3\text{OH}(\text{NH}_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.65 grams (45.4%) of
35 9-fluoro-6,11-dihydro-11-[1-(3-methyl-2-butenyl)-4-piperidinyldene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 203.4°C (comp. 2.04).

Example 32

A mixture of 1.5 grams of 3-bromo-1-propene, 2.65 grams of compound (1.04), 1.0 gram of sodium hydrogen carbonate and 100 ml of ethanol was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH} / \text{CH}_3\text{OH}(\text{NH}_3)$ 90:10:0 \rightarrow 90:10:1). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried for 2 hours in vacuo at 100°C, yielding 1.1 grams (20.5%) of 6,11-dihydro-11-[1-(2-propenyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 160.8°C (comp. 1.07).

Example 33

A mixture of 2.7 grams of compound (3.04), 1 gram of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and 50°C in the presence of 1 gram of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH}(\text{NH}_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in 2-propanol. The salt was filtered off and dried, yielding 3.1 grams (59.0%) of 6,11-dihydro-8-methyl-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 211.0°C (comp. 3.05).

Example 34

A mixture of 2.7 grams of compound (5.01), 2 grams of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and room temperature in the presence of 2 grams of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was partitioned between dichloromethane and NH_4OH . The aqueous layer was separated and re-extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was crystallized from a mixture of 2,2'-oxybispropane and acetonitrile (2x). The product was filtered off and dried, yielding 0.76 grams (26.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinyl)-5H-imidazo[2,1-b][3]benzazepine hemihydrate; mp. 117.8°C (comp. 5.02).

Example 35

A mixture of 2.65 grams of compound (1.04), 20 ml of acetic acid and 15 ml of 2-propanone was stirred for 2 hours at room temperature under nitrogen. There were
5 added portionwise 1.5 grams of sodium tetrahydroborate and stirring was continued for 18 hours. The reaction mixture was diluted with water and basified with NaOH 15%. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH / CH₃OH(NH₃) 90:10:1). The eluent of the desired fraction was evaporated
10 and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.5 grams (46.3%) of 6,11-dihydro-11-[1-(1-methylethyl)-4-piperidinyldene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 183.6°C (comp. 1.06).

15 Example 36

A mixture of 4 grams of compound (4.03), 2 ml of acetic acid, 3 grams of sodium acetate and 20 ml of formaldehyde 37% was stirred for 50 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole
20 was basified with NaOH (aq.) and extracted with a mixture of dichloromethane and methanol. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH(NH₃) 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of acetonitrile and 2,2'-oxybispropane. The product was
25 filtered off and dried, yielding 0.4 grams (9.2%) of 6,11-dihydro-3-methyl-11-(1-methyl-4-piperidinyldene)-5H-imidazo[2,1-b][3]benzazepine-2-methanol; mp. 166.8°C (comp. 4.21).

Example 37

A mixture of 1.6 grams of (2-pyridinyl)ethene, 2.7 grams of compound (5.01) and 100
30 ml of 1-butanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH / CH₃OH:NH₃ 90:10:1). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.7 grams (45.6%) of 6,11-dihydro-11-[1-[2-(2-pyridinyl)ethyl]-4-piperidinyldene]-5H-imidazo[2,1-b][3]benzazepine; mp. 170.3°C (comp. 5.04).
35

Example 38

Through a stirred mixture of 32 grams of compound (1.04) and 300 ml of methanol was bubbled gaseous oxirane for 1 hour at room temperature. After stirring for 3 hours at room temperature, the mixture was purified by column chromatography (silica gel ;
5 $\text{CH}_2\text{Cl}_2 / \text{CH}_3\text{OH} / \text{CH}_3\text{OH}:\text{NH}_3$ 90:10:0 \rightarrow 90:10:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in acetonitrile. The salt was filtered off and dried, yielding 15 grams (23.1%) of
4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineethanol
(Z)-2-butenedioate(1:2); mp. 145.7°C (comp. 1.30).

10

Example 39

A solution of 9.6 grams of compound (4.08) in 300 ml of methanol/ NH_3 was hydrogenated in the presence of 3 grams of Raney Nickel catalyst. After complete reaction, the catalyst was filtered off and the filtrate was evaporated, yielding 12.5 grams
15 (100%) of 4-(5,6-dihydro-3-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineethanamine (comp. 4.09).

Example 40

0.57 Grams of lithium aluminum hydride were added portionwise to 100 ml of tetrahydrofuran under nitrogen. A solution of 2.3 grams of compound (1.26) in tetrahydrofuran was added dropwise and the reaction mixture was stirred for 3 hours at reflux temperature. The mixture was decomposed with 2 ml of water, 2 ml of a sodium hydroxide solution 15% and 2 parts of water. After filtration over diatomaceous earth,
20 the filtrate was evaporated, yielding 2.3 grams (97.5%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-yl)-1-piperidineethanamine (comp. 5.07).
25

Example 41

A solution of 3.1 grams of compound (1.30) in N,N-dimethylacetamide was added dropwise to a mixture of 0.7 grams of a sodium hydride dispersion 50% and 200 ml of
30 N,N-dimethylacetamide under nitrogen and at room temperature. After stirring for 1 hour, 1.1 grams of 2-chloropyrimidine were added and the whole was stirred for 16 hours at room temperature. The reaction mixture was decomposed with water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; $\text{CH}_2\text{Cl}_2 /$
35 CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 1.4 grams (22.6%) of 6,11-dihydro-11-[1-[2-(2-pyrimidinyl)oxy]ethyl]-

4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate(1:2);
mp. 172.6°C (comp. 1.31).

Example 42

- 5 A mixture of 3.3 grams of 2-chloropyrimidine, 3.2 grams of compound (4.09), 1.26 grams of sodium hydrogen carbonate and 200 ml of ethanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ;
10 CH₂Cl₂ / CH₃OH 95:5 → 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.56 grams (63.9%) of N-[2-[4-(5,6-dihydro-3-methyl-11H-imidazo[2,1-b]-[3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-2-pyrimidinamine; mp. 171.3°C (comp. 4.10).

Example 43

- 15 A mixture of 2.0 grams of 5-bromo-1,3,4-thiadiazole-2-amine, 3.42 grams of compound (1.27), 1.2 grams of sodium carbonate, 0.01 grams of potassium iodide and 200 ml of N,N-dimethylacetamide was stirred for 4 hours at 120°C. The reaction
20 mixture was evaporated and the residue was stirred in dichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH / CH₃OH:NH₃ 90:10:1 → 90:7:3). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile and ethanol. The product was filtered off and dried, yielding 1.62 grams
25 (36.2%) of N²-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1,3,4-thiadiazole-2,5-diamine; mp. 251.4°C (comp. 1.33).

Example 44

- 30 To a stirred mixture of 1.1 grams of 3-furancarboxylic acid, 1.9 grams of N,N-diethylethanamine and 200 ml of dichloromethane were added portionwise 2.4 grams of 2-chloro-1-methylpyridinium iodide. After stirring for 1 hour at room temperature, a solution of 2.9 parts of compound (1.27) in dichloromethane was added dropwise. Upon completion, the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was basified with K₂CO₃(aq) and extracted with dichloromethane.
35 The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 94:6 → 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in

2-propanone. The salt was filtered off and dried, yielding 1.88 grams (31.5%) of *N*-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-3-furancarboxamide (Z)-2-butenedioate(1:2); mp. 202.9°C (comp. 1.35).

5 Example 45

A mixture of 0.6 grams of isocyanatomethane, 3.1 grams of compound (1.27) and 100 ml of tetrahydrofuran was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was crystallized from acetonitrile. The precipitated product was filtered off and dried, yielding 2.0 grams (54.7%) of *N*-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-*N'*-methylurea; mp. 178.1°C (comp. 1.36).

Example 46

- 15 a) To a stirred and cooled (-10°C) mixture of 18 grams of carbon disulfide, 7.22 grams of *N,N*-methanetetraylbis(cyclohexanamine) and 150 ml of tetrahydrofuran was added dropwise a solution of 10.8 grams of compound (1.27) in tetrahydrofuran. After stirring for 1 hour at room temperature, the reaction mixture was evaporated, yielding 12 grams (97.5%) of 6,11-dihydro-11-[1-(2-isothiocyanatoethyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (comp. 1.37).
- 20 b) A mixture of 2.7 grams of 3,4-pyridinediamine, 8.8 grams of compound (1.37) and 150 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature. To the obtained reaction mixture were added 7.6 grams of mercury(II)oxide, 0.01 grams of sulfur and 150 ml of tetrahydrofuran. After refluxing for 5 hours, the reaction mixture was filtered while hot over diatomaceous earth and the filtrate was evaporated. The
- 25 residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH / CH₃OH:NH₃ 90:5:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate salt in methanol. The salt was filtered off and dried, yielding 1.65 grams (14.4%) of *N*-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-1H-imidazo[4,5-c]pyridin-2-amine
- 30 (E)-2-butenedioate(1:3) hemihydrate; mp. 203.0°C (comp. 1.39).

Example 47

- 35 1 Gram of gaseous methanamine was bubbled through 100 ml of tetrahydrofuran. A solution of 3.5 grams of compound (1.37) in tetrahydrofuran was added and the reaction mixture was stirred for 2 hours at room temperature. After evaporation, the residue was purified by column chromatography (silica gel; CH₂Cl₂ / CH₃OH / CH₃OH:NH₃ 90:10:0 → 90:10:1). The eluent of the desired fraction was evaporated and the residue

was crystallized from 2,2'-oxybispropane. The crystallized product was filtered off and dried, yielding 0.9 grams (23.0%) of N-[2-[4-(5,6-dihydro-1H-imidazo[2,1-b][3]-benzazepin-11-ylidene)-1-piperidinyl]ethyl]-N'-methylthiourea hemihydrate; mp. 155.2°C (comp. 1.40).

5

Example 48

a) A mixture of 7.6 grams of compound (1.30) and 100 ml of thionyl chloride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was stirred in methylbenzene (2x). The obtained residue was dissolved in water and treated with sodium carbonate. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 0.7 grams (5%) of 11-[1-(2-chloroethyl)-4-piperidinylidene]-6,11-dihydro-5H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 169.9°C (comp. 1.41).

15

b) A mixture of 2.8 grams of 1-methyl-1H-imidazol-2-thiol, 6.5 grams of compound (1.41), 8.3 grams of potassium carbonate and 200 ml of 2-propanone was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated, the residue was taken up in dichloromethane, washed with water, dried, filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 90:10). The eluent of the desired fraction was evaporated and the residue was taken up in methylbenzene and treated with activated charcoal. The whole was filtered while hot, the filtrate was allowed to cool and was then evaporated. The residue was converted into the cyclohexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 1.6 grams (10.5%) of 6,11-dihydro-11-[1-[2-[(1-methyl-1H-imidazol-2-yl)thio]ethyl]-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine cyclohexane-sulfamate (1:2); mp. 265.4°C (decomp.) (comp. 1.42).

20

25

30 Example 49

A mixture of 9.6 grams of methyl N-(2,2'-dimethoxyethyl)-N'-methylcarbamimidothioate hydroiodide, 9.3 grams of compound (1.27) and 200 ml of 2-propanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was stirred in 200 parts of a hydrochloric acid solution 1N. After stirring for 18 hours at room temperature, the whole was treated with potassium carbonate and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography HPLC (silica gel ;

35

CHCl₃ / CH₃OH 98:2). The eluent of the desired fraction was evaporated and the residue was converted into the cyclohexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 0.71 grams (3%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-N-(1-methyl-1H-imidazol-2-yl)-1-piperidine-ethanamine cyclohexanesulfamate (1:3) dihydrate; mp. 153.9°C (comp. 1.44)

Example 50

A mixture of 1.42 grams of 2-mercapto-4-pyrimidinone, 3.1 grams of compound (1.27) and 1 ml of N,N-dimethylacetamide was stirred for 4 hours at 140°C. After cooling, the mixture was purified by column chromatography (silica gel ; CHCl₃ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanone. The salt was filtered off and dried in a dry pistol, yielding 1.8 grams (32.9%) of 2-[[2-[4-(5,6-dihydro-11H-imidazo-[2,1-b][3]-benzazepin-11-ylidene)-1-piperidinyl]ethyl]amino]-4(1H)-pyrimidinone trihydrochloride dihydrate; mp. 234.8°C (comp. 1.45).

Example 51

A mixture of 1 gram of compound (4.11), 5 grams of manganese(IV)oxide and 100 ml of trichloromethane was stirred for 2 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth. After evaporation, the residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 1,1'-oxybis-ethane. The product was filtered off and dried, yielding 0.48 grams (48.6%) of ethyl 4-(3-formyl-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-carboxylate; mp. 138.2°C (comp. 4.15).

Example 52

To a stirred solution of 9.7 grams of compound (4.15) in 100 ml of water was added dropwise a solution of 13.7 grams of AgNO₃ in 50 ml of water and then a solution of 13.3 grams of potassium hydroxide in 50 ml of water. After stirring for 18 hours, the reaction mixture was filtered and the filtrate acidified with hydrochloric acid. After evaporation, the residue was stirred in methanol, the precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel ; NH₄OAc / H₂O / CH₃OH 55:0.5:45). The eluent of the desired fraction was evaporated and the residue was stirred in 2-propanone and activated charcoal. The precipitate was filtered off and the filtrate was evaporated. The residue was crystallized first from 2,2'-oxybispropane and then from acetonitrile. The product was filtered off and dried.

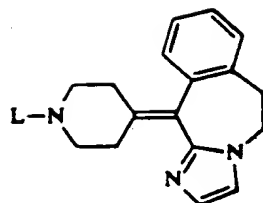
yielding 0.3 grams (3%) of 11-[1-(ethoxycarbonyl)-4-piperidinylidene]-6,11-dihydro-5H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid; mp. 182.2°C (comp. 4.17).


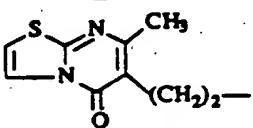
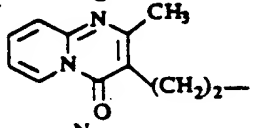
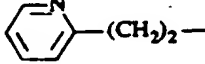
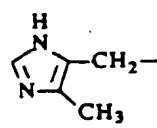
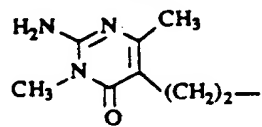
Example 53

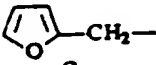
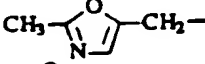
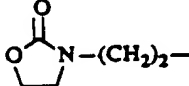
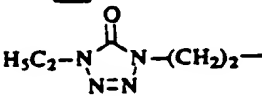
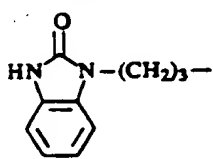
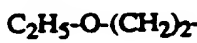
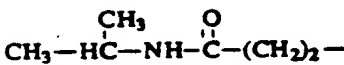


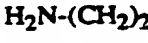
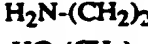
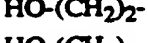
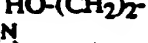
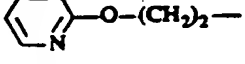
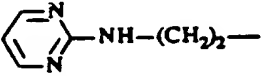
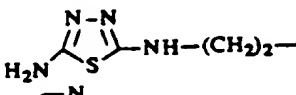
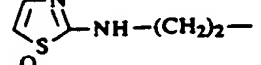
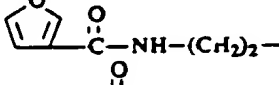
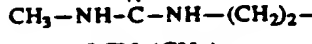
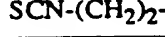
- 5 To a stirred mixture of 2.93 grams of compound (4.03), 1.3 grams of sodium acetate and 30 ml of acetic acid was added dropwise a solution of 1.6 grams of bromine in 20 ml of acetic acid. After stirring for 1 hour at 30°C, the mixture was evaporated and the residue was taken up in water. The aqueous solution was treated with sodium hydroxide and the product was extracted with dichloromethane. The extract was dried,
- 10 filtered and evaporated. The residue was purified by column chromatography (silica gel ; CH₂Cl₂ / CH₃OH 95:5 → CH₂Cl₂ / CH₃OH / CH₃OH:NH₃ 90:8:2). The eluent of the desired fraction was evaporated and the residue was boiled in acetonitrile. After cooling, the precipitated product was filtered off and dried, yielding 0.96 grams (25.8%)
- 15 of 2-bromo-6,11-dihydro-3-methyl-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine; mp. 116.0°C (comp. 4.22).

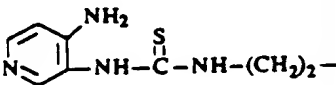
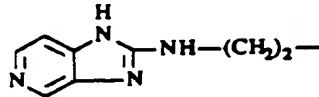
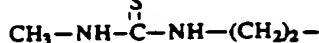
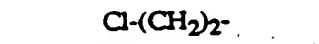
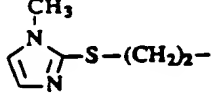
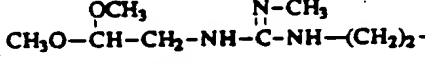
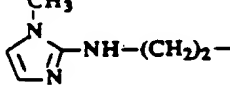
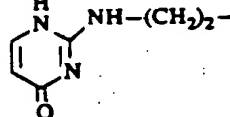
All compounds listed in Tables 1-6 were prepared following methods of preparation described in examples 13-53, as is indicated in the column Ex. No.

Table 1



Co. No.	Ex. No.	L	Physical data
1.01	13	CH ₃ -	mp. 209.3°C / CF ₃ SO ₃ H
1.02	13	CH ₃ -	mp. 154.5°C
1.03	19	H ₅ C ₂ OOC-	mp. 170.6°C
1.04	21	H-	mp. 192.5°C / 1/2 H ₂ O . 2(E)*
1.05	34	C ₂ H ₅ -	mp. 184.2°C / 2(Z)*
1.06	35	CH ₃ CH(CH ₃)-	mp. 183.6°C / 2(Z)*
1.07	32	CH ₂ =CH-CH ₂ -	mp. 160.8°C / 2(Z)*
1.08	28	CH ₂ =C(CH ₃)-CH ₂ -	mp. 179.5°C / 3/2(E)*
1.09	29	CH ₃ -C(CH ₃)=CH-CH ₂ -	mp. 127.2°C
1.10	25	C ₆ H ₅ -CH=CH-CH ₂ -	mp. 172.2°C / (E)
1.11	33	C ₆ H ₅ -CH ₂ -	mp. 207.2°C
1.12	26	CH ₃ O-  -(CH ₂) ₂ -	mp. 180.5°C / 2(COOH) ₂
1.13	26		mp. 181.8°C
1.14	25		mp. 197.8°C / H ₂ O . 3(E)*
1.15	37		mp. 163.8°C
1.16	28		mp. 199.0°C
1.17	25		mp. 257.4°C

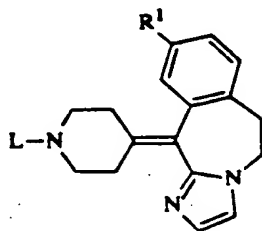
Co. No.	Ex. No.	L	Physical data
1.18	34		mp. 160.3°C
1.19	26		mp. 162.1°C / H ₂ O . 2(E)*
1.20	25		mp. 188.8°C / 3/2(E)*
1.21	25		mp. 170.7°C / 2(Z)*
1.22	25		mp. 194.7°C
1.23	25		mp. 176.5°C / 2(Z)*
1.24	25		mp. 165.5°C
1.25	25		mp. 167.2°C / 2(E)*
1.26	27		mp. 220.4°C
1.27	21		-
1.28	39		mp. 186.6°C / 1/2 H ₂ O . 3(E)*
1.29	38		mp. 225.1°C / CF ₃ SO ₃ H
1.30	38		mp. 145.7°C / 2(Z)*
1.31	41		mp. 172.6°C / 2(Z)*
1.32	42		mp. 165.1°C
1.33	43		mp. 251.4°C
1.34	43		mp. 205.5°C / 1/2 H ₂ O / 4**
1.35	44		mp. 202.9°C / 2(Z)*
1.36	45		mp. 178.1°C
1.37	46		

Co. No.	Ex. No.	L-	Physical data
1.38	46		-
1.39	46		mp. 203.0°C / 1/2H ₂ O . 3(E)*
1.40	47		mp. 155.2°C / 1/2H ₂ O
1.41	48		mp. 169.9°C / 2(Z)*
1.42	48		mp. 265.4°C (dec.) / 2**
1.43	49		HI
1.44	49		mp. 153.9°C / 2H ₂ O . 3**
1.45	50		mp. 234.8°C / 2H ₂ O . 3HCl

* : 2-butenedioate

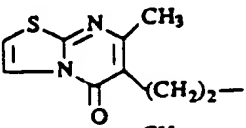
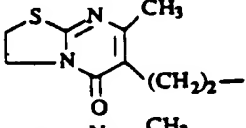
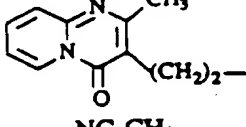
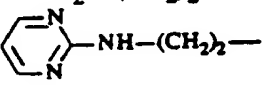
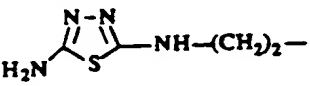
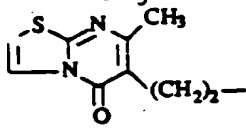
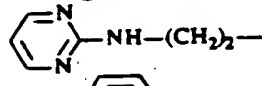
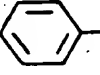
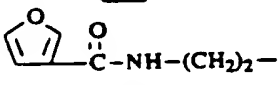
** : cyclohexanesulfamate

Table 2



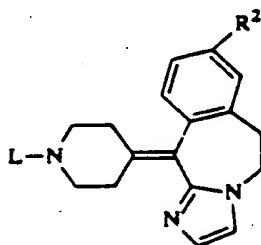
5

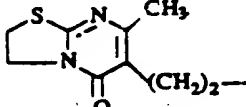
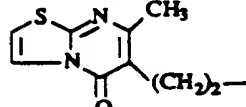
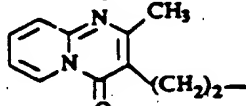
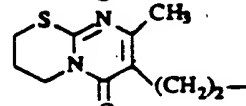
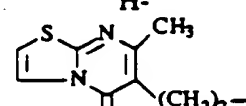
Co. No.	Ex. No.	L-	R ¹	Physical data
2.01	13	CH ₃ -	F	mp. 195.7°C / 2(E)*
2.02	19	H ₅ C ₂ OOC-	F	mp. 175.2°C
2.03	21	H-	F	mp. 180.1°C
2.04	31	CH ₃ -C(CH ₃)=CH-CH ₂ -	F	mp. 203.4°C / 2(Z)*

Co. No.	Ex. No.	L-	R ¹	Physical data
2.05	25		F	mp. 168.9°C / 3/2 H ₂ O . 5/2(E)*
2.06	25		F	mp. 162.2°C / 3/2 H ₂ O . 5/2(E)*
2.07	25		F	mp. 201.9°C / 3(E)*
2.08	30	NC-CH ₂ -	F	mp. 198.3°C
2.09	39	H ₂ N-(CH ₂) ₂ -	F	-
2.10	42		F	mp. 165.1°C / 3(Z)*
2.11	43		F	mp. 238.6°C
2.12	13	H-	CH ₃ -	mp. 203.1°C
2.13	24	H ₅ C ₂ OOC-	CH ₃ -	mp. 156.5°C
2.14	33	CH ₃ -	CH ₃ -	mp. 214.3°C
2.15	26		CH ₃ -	mp. 202.2°C
2.16	30	NC-CH ₂ -	CH ₃ -	-
2.17	39	H ₂ N-(CH ₂) ₂ -	CH ₃ -	mp. 219.3°C / 3(E)*
2.18	42		CH ₃ -	mp. 131.1°C
2.19	26	CH ₃ O-  -(CH ₂) ₂ -	CH ₃ -	mp. 192.6°C / 5/2(COOH) ₂
2.20	44		CH ₃ -	mp. 214.2°C / 2(Z)*
2.21	13	CH ₃ -	Br	mp. 213.4°C

* : 2-butenedioate

Table 3



Co. No.	Ex. No.	L	R ²	Physical data
3.01	14	CH ₃ -	CH ₃ O-	mp. 190.3°C / 2(Z)*
3.02	19	H ₅ C ₂ OOC-	CH ₃ O-	mp. 104.4°C
3.03	21	H-	CH ₃ O-	mp. 184.4°C
3.04	13	H-	CH ₃ -	mp. 221.9°C / 2(E)*
3.05	33	CH ₃ -	CH ₃ -	mp. 211.0°C / 2(E)*
3.06	25		CH ₃ -	mp. 199.8°C
3.07	25		CH ₃ -	mp. 214.2°C
3.08	25		CH ₃ -	mp. 162.3°C / H ₂ O . 3(E)*
3.09	25		CH ₃ -	mp. 235.1°C / 2H ₂ O . 3HCl
3.10	13	CH ₃ -	Cl	mp. 186.6°C
3.11	19	H ₅ C ₂ OOC-	Cl	mp. 140.3°C
3.12	23	H-	Cl	mp. 197.1°C
3.13	26		Cl	mp. 217.6°C
3.14	30	NC-CH ₂ -	Cl	-
3.15	15	CH ₃ -	F	mp. 152.4°C
3.16	19	H ₅ C ₂ OOC-	F	mp. 149.4°C
3.17	21	H-	F	-

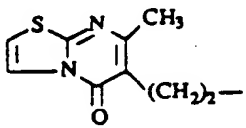
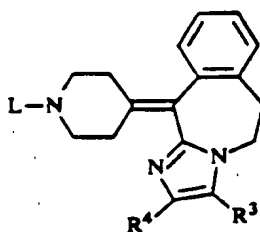
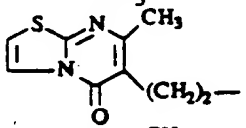
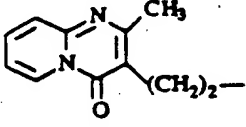
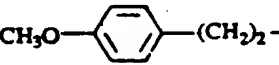
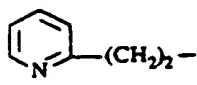
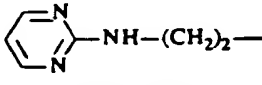


Co. No.	Ex. No.	L	R ²	Physical data
3.18	26		F	mp. 192.2°C / H ₂ O . 3/2(E)*

Table 4

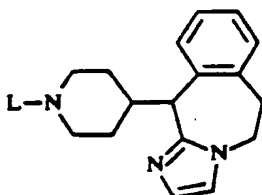


Co. No.	Ex. No.	L	R ³	R ⁴	Physical data
4.01	17	CH ₃ -	H	C ₆ H ₅	mp. 171.5 °C
4.02	13	H	-CH ₃	H	mp. 167.0 °C
4.03	33	CH ₃ -	-CH ₃	H	mp. 172.2 °C
4.04	25		-CH ₃	H	mp. 212.4 °C
4.05	25		-CH ₃	H	mp. 186.3 °C / 3 (E)* H ₂ O
4.06	25	CH ₃ O- 	-CH ₃	H	mp. 150.6 °C / 5/2(COOH) ₂ H ₂ O
4.07	37		-CH ₃	H	mp. 180.2 °C / 7/2(COOH) ₂
4.08	30	NC-CH ₂ -	-CH ₃	H	mp. 226.5 °C
4.09	39	H ₂ N-(CH ₂) ₂ -	-CH ₃	H	-
4.10	42		-CH ₃	H	mp. 171.3 °C
4.11	20	C ₂ H ₅ OOC-	-CH ₂ OH	H	mp. 191.9 °C
4.12	21	H	-CH ₂ OH	H	mp. >200 °C dec. 5/2 (E)*


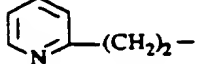
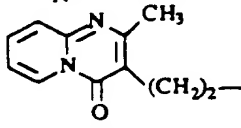
Co. No.	Ex. No.	L ⁻	R ³	R ⁴	Physical data
4.13	33		-CH ₂ OH	H	mp. 228.3 °C
4.14	26		-CH ₂ OH	H	-
4.15	51	C ₂ H ₅ OOC-	-CHO	H	mp. 138.2 °C
4.16	51	CH ₃ -	-CHO	H	mp. 171.6 °C
4.17	52	C ₂ H ₅ OOC-	-COOH	H	mp. 182.2 °C
4.18	20	C ₂ H ₅ OOC-	-CH ₂ OH	-CH ₂ OH	-
4.19	21	H-	-CH ₂ OH	-CH ₂ OH	-
4.20	33	CH ₃ -	-CH ₂ OH	-CH ₂ OH	mp. 206.3 °C
4.21	36	CH ₃ -	-CH ₃	-CH ₂ OH	mp. 166.8 °C
4.22	53	CH ₃ -	-CH ₃	-Br	mp. 116.0 °C

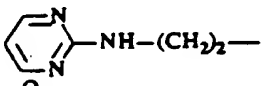
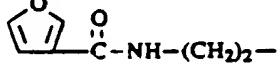
* = 2-butenedioate

Table 5



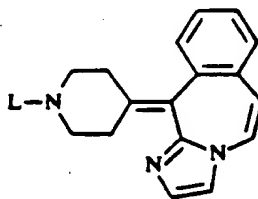
5

Co. No.	Ex. No.	L ⁻	Physical data
5.01	16	H-	mp. 220.2 °C / 2 (E)*
5.02	34	CH ₃ -	mp. 117.8 °C / 1/2 H ₂ O
5.03	25		mp. 221.6 °C / 2 (COOH) ₂ / 1/2 H ₂ O
5.04	37		mp. 170.3 °C
5.05	25		mp. 193.3 °C
5.06	27	NC-CH ₂ -	mp. 194.7 °C / 1/2 (E)*

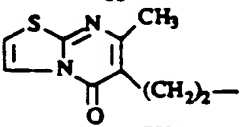
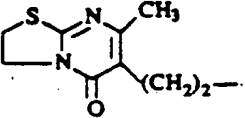
Co. No.	Ex. No.	L	Physical data
5.07	40	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-$	-
5.08	42		mp. 175.1 °C / 7/2 (E)*
5.09	44		mp. 203.5 °C

* = 2-butenedioate

Table 6

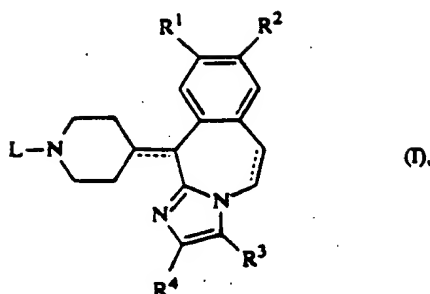


5

Co. No.	Ex. No.	L	Physical data
6.01	18	CH_3-	mp. 135.8 °C
6.02	19	$\text{C}_2\text{H}_5\text{OOC}-$	-
6.03	22	$\text{H}-$	mp. 246.9 °C / 2HBr 1/2 H ₂ O
6.04	27		mp. 206.4 °C / 2(COOH) ₂ 1/2 H ₂ O
6.05	26		mp. 158.9 °C / 5/2(COOH) ₂ 1/2 H ₂ O

Claims

1. A compound having the formula



5

a pharmaceutically acceptable addition salt and stereochemically isomeric form thereof, wherein

each of the dotted lines independently represents an optional bond ;

10

R^1 represents hydrogen, halo or C_{1-4} alkyl;

R^2 represents hydrogen, halo, C_{1-4} alkyl or C_{1-4} alkyloxy ;

R^3 represents hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, formyl or hydroxycarbonyl ;

R^4 represents hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, phenyl or halo ;

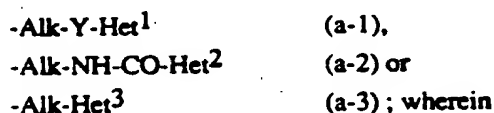
15

L represents hydrogen; C_{1-6} alkyl; C_{1-6} alkyl substituted with hydroxy, C_{1-4} alkyloxy, C_{1-4} alkyloxycarbonylamino, C_{1-4} alkylaminocarbonyl, C_{1-4} alkylaminocarbonylamino, C_{1-4} alkylaminothiocabonylamino, aryl or aryloxy; C_{3-6} alkenyl; C_{3-6} alkenyl substituted with aryl ;

wherein each aryl is phenyl or phenyl substituted with halo, C_{1-4} alkyl or C_{1-4} alkyloxy ; or,

20

L represents a radical of formula



25

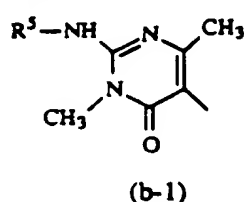
Alk represents C_{1-4} alkanediyl ;

Y represents O, S or NH ;

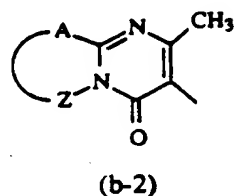
Het¹, Het² and Het³ each represent furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4} alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4} alkyl pyridinyl,

30

pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C₁₋₄alkyl, C₁₋₄alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



or



wherein

R⁵ represents hydrogen or C₁₋₄alkyl; and

10 A-Z represents S-CH=CH, S-CH₂-CH₂, S-CH₂-CH₂-CH₂, CH=CH-CH=CH or CH₂-CH₂-CH₂-CH₂.

2. A compound according to claim 1 wherein L represents hydrogen; C₁₋₄alkyl; C₁₋₄alkyl substituted with hydroxy, C₁₋₄alkyloxy, C₁₋₄alkylaminocarbonyl, C₁₋₄alkylaminocarbonylamino, C₁₋₄alkylaminothiocarbonyl-amino or aryl; propenyl; propenyl substituted with aryl; wherein each aryl is phenyl or phenyl substituted with C₁₋₄alkyloxy; or,

15

L represents a radical of formula (a-1), (a-2) or (a-3); wherein Het¹, Het² and Het³ represent furanyl, thiazolyl or imidazolyl each optionally substituted with one or two C₁₋₄alkyl substituents; pyridinyl or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and Het³ may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C₁₋₄alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula (b-1) or (b-2), wherein R⁵ represents hydrogen; and A-Z represents S-CH=CH, S-CH₂-CH₂ or CH=CH-CH=CH.

20

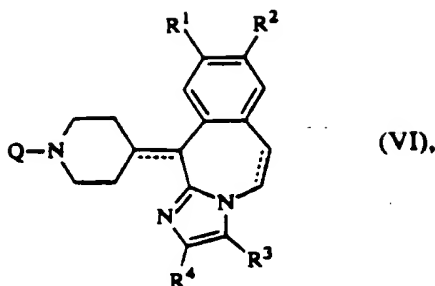
25

3. A compound according to claim 1 wherein R² represents halo, C₁₋₄alkyl or C₁₋₄alkyloxy; and R⁴ represents hydrogen, C₁₋₄alkyl, hydroxyc₁₋₄alkyl or halo.

30

4. A compound according to any of claims 1 to 3 wherein L is C₁₋₄alkyl.

5. A compound having the formula

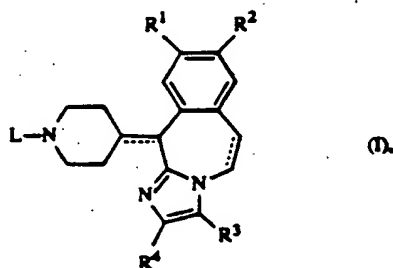


- 5 an acid addition salt thereof or a stereochemically isomeric form thereof, wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1 ;
Q is (C₁₋₆alkyl or phenyl)oxycarbonyl or C₁₋₆alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)aminothiocarbonylamino or (CH₃O)₂CH-CH₂-NH-C(=NCH₃)-NH-.
- 10 6. A compound according to claim 5 wherein Q represents C₁₋₄alkyloxycarbonyl, a pharmaceutically acceptable acid addition salt thereof or a stereochemically isomeric form thereof.
- 15 7. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable carrier.
- 20 8. A method of preparing a pharmaceutical composition as claimed in claim 7, characterized in that a therapeutically effective amount of a compound as claimed in claim 1 is intimately mixed with a pharmaceutical carrier.
- 25 9. A method of treating subjects suffering from allergic disorders said method comprising administering to said subjects an effective antiallergic amount of a compound as claimed in claim 1.

ABSTRACT

IMIDAZO[2,1-b][3]BENZAZEPINE DERIVATIVES,
COMPOSITIONS AND METHOD OF USE

The present invention is concerned with novel imidazo[2,1-b][3]benzazepines of formula



the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein

- each of the dotted lines independently represents an optional bond ;
 R^1 represents hydrogen, halo or C_{1-4} alkyl;
 R^2 represents hydrogen, halo, C_{1-4} alkyl or C_{1-4} alkyloxy ;
 R^3 represents hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, formyl or hydroxycarbonyl ;
 R^4 represents hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, phenyl or halo ;
 L represents hydrogen; C_{1-6} alkyl; C_{1-6} alkyl substituted with hydroxy, C_{1-4} alkyl-
 oxy, C_{1-4} alkyloxycarbonylamino, C_{1-4} alkylaminocarbonyl, C_{1-4} alkylamino-
 carbonylamino, C_{1-4} alkylaminothiocarbonylamino, aryl or aryloxy; C_{3-6} alkenyl;
 C_{3-6} alkenyl substituted with aryl ;
 wherein each aryl is phenyl or phenyl substituted with halo, C_{1-4} alkyl or
 C_{1-4} alkyloxy ; or,
 L represents a radical of formula
- | | |
|-----------------------------|----------|
| -Alk-Y-Het ¹ | (a-1), |
| -Alk-NH-CO-Het ² | (a-2) or |
| -Alk-Het ³ | (a-3) ; |

which are useful antiallergic compounds.

Compositions comprising said compounds and methods of using the same.

JAB 758

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**IMIDAZO[2,1-b][3]BENZAZEPINE DERIVATIVES,
COMPOSITIONS AND METHOD OF USE**

the specification of which

(check one) ☒ [X] is attached hereto.

[] was filed on , 1991 as

Application Serial No.

and was amended on

(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119
		Day/Mo./Year	<input type="checkbox"/> YES <input type="checkbox"/> NO
		Day/Mo./Year	<input type="checkbox"/> YES <input type="checkbox"/> NO
		Day/Mo./Year	<input type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending, abandoned)
Application Serial No.	Filing Date	Status (patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Robert L. Minier (Reg. #20,083), Audley A. Ciamporcero, Jr. (Reg. #26,051), Steven P. Berman (Reg. #24,772), Jason Lipow (Reg. #25,509), and Charles J. Metz (Reg. #20,359).

Address all telephone calls to Charles J. Metz at telephone no. (201) 524-2814.

JAB 758

Address all correspondence to ⁶⁰¹Robert L. Minier, ⁶⁰²One Johnson &
Johnson Plaza, New Brunswick, NJ 08933-7003.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Inventor's Signature:
Full Name of First Inventor :

Date :

Franc E. Janssens

June 4th, 1991

Citizenship : Belgium
Residence : B-2820-Bonheiden, Belgium
Post Office Address : Tinststraat 79

BEX

Inventor's Signature:
Full Name of Second Joint Inventor:

Date :

Gaston S./M. Diels

June 4th, 1991

Citizenship : Belgium
Residence : B-2380-Ravels, Belgium
Post Office Address : Oosteinde 12

BEX

Inventor's Signature:
Full Name of Third Joint Inventor:

Date :

Joseph E. Leenaerts

June 4th, 1991

Citizenship : Belgium
Residence : B-2310-Rijkevorsel, Belgium
Post Office Address : Potbergstraat 35

BEX